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…New Horizons…

As a new year begins, setting new goals and starting the implementation of new plans is mandatory. We are lucky to experience an evolutionary leap in the field of neurology all over the world, in research as well as in management and treatment of neurological diseases. Our country already started following trend by introducing the first Stroke Units in public hospitals, and new horizons open, presenting with bright possibilities for the future.

This is the first issue of 2024, and contains five articles, all of them in English, further supporting our attempt to broaden the readers' appeal of our journal and to integrate the Archives of Clinical Neurology in the PUBMED inventory.

In the first review by Chatzistefanidis et al., an outline of the evolution of neurocritical care in the past decades in presented. The palpable results in the ameliorated clinical outcome of the patients are highlighted and the significant role of neurointensivists as a part of interdisciplinary teams is stressed.

Mysiris et al. present a case report with respiratory failure as the initial clinical manifestation of myasthenia gravis in the intensive care unit. Myasthenia gravis and more specifically myasthenic crisis is a dreaded comorbidity in medical practice, and a high index of suspicion should exist in cases of otherwise unexplained respiratory failure of difficulty in weaning from mechanical ventilation , especially in young adults.

Tsouris et al. showcased a female patient with myelin oligodendrocyte antibody associated disease and her clinical and radiological disease progression which was unexpectedly combined with disease progression between her disease relapses, supporting the fact that the myelin oligodendrocyte antibody associated disease has a highly heterogeneous clinical profile and should be kept in mind as a differential in central nervous system demyelinating diseases.

In the next article, Tsantzali et al. presented an interesting case series of four patients phenotypically suggesting the diagnosis of Alzheimer's disease, whose cerebrospinal fluid biormarkers did not support the diagnosis, indicating that when disease specific treatments are available, laboratory confirmation of this common disease should be pursued.

Finally, in the last review by Kyziridis, the existing literature regarding lamotrigine induced hemophagotic lymphohistiocytosis is discussed, which is a significant side effect of lamotrigine administration, presenting within the first three weeks independent of medication dose. Appropriate management considerations are outlined in detail.

In the beginning of this year, I would like to thank you all for your continued support to our journal and further motivate you to broaden your horizons, set new goals and collaborate with each other, in order to achieve the best for our patients and for our journal.

GEORGIOS TSIVGOULIS
Professor of Neurology
National and Kapodistrian University of Athens

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Δημήτριος Χατζηστεφανίδης[1], Σπυρίδων Κονιτσιώτης[1]

[1] *Τμήμα Νευρολογίας, Τμήμα Ιατρικής Σχολής, Σχολή Επιστημών Υγείας, Πανεπιστήμιο Ιωαννίνων, Ιωάννινα, Ελλάδα*

Περίληψη

Η νοσηλεία ασθενών σε εξειδικευμένες μονάδες νευροεντατικής θεραπείας έχει εξελιχθεί τις τελευταίες δεκαετίες και αποτελεί πλέον ξεχωριστά οργανωμένη ειδικότητα σε πολλά συστήματα υγείας. Η νευροεντατική θεραπεία χρησιμοποιεί ομάδες πολλαπλών ειδικοτήτων, γίνεται χρήση συγκεκριμένων πρωτοκόλλων θεραπείας και παρακολούθησης νευρολογικών λειτουργιών, καθώς επίσης διεξάγει έρευνα και αναπτύσσει περαιτέρω η ίδια το πεδίο αυτό. Το φάσμα της έχει επεκταθεί σημαντικά και οι τεχνολογικές εξελίξεις επιτρέπουν τη δυνατότητα παράλληλης παρακολούθησης των νευρολογικών λειτουργιών με διάφορους τρόπους, αν και το τελικό αποτέλεσμα στη διαχείριση των ασθενών και την λειτουργική τους κατάσταση απαιτεί περαιτέρω έρευνα. Αν και υπάρχουν σαφή στοιχεία ότι η νευροεντατική θεραπεία μπορεί να βελτιώσει την έκβαση και την ποιότητα ζωής των ασθενών που είναι σοβαρά άρρωστοι, η κατανόηση της δομής της, της κλινικής της εφαρμογής και την ταυτόχρονης παρακολούθησης των νευρολογικών λειτουργιών μέσω διαφορετικών μεθόδων είναι ουσιαστική για την περαιτέρω εξέλιξη το τομέα. Για τον λόγο αυτό, παρουσιάζουμε εδώ την ιστορική εξέλιξη των μονάδων νευροεντατικής φροντίδας και της σύγχρονης δομής τους, όπως και το φάσμα των ασθενειών που νοσηλεύονται σε αυτή, καθώς και τις διαθέσιμες δυνατότητες παρακολούθησης της νευρολογικής λειτουργίας.

Λέξεις ευρετηρίου: neurointensive care units, multimodal neuromonitoring, neurointensivist / νευροεντατική θεραπεία, πολυπαραγοντική παρακολούθηση νευρολογικής λειτουργίας, νευροεντατικολόγος

GENERAL ORGANIZATION, DISEASE SPECTRUM AND MULTIMODAL MONITORING IN NEUROCRITICAL CARE UNITS; A REVIEW

Dimitrios Chatzistefanidis[[1]], Spyridon Konitsiotis[[1]]

[[1]] *Department of Neurology, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece.*

Abstract

Neurocritical care has further evolved in the last decades and is currently part of many health systems as separately organized specialty. Neurocritical care involves interdisciplinary teams, protocol implementation and neuromonitoring as well as research and further development of the filed. Its spectrum has drastically been expanded and technological developments have improved multimodal monitoring capacities, although its impact on patients' management and functional status requires further research. Although there is clear evidence that neurocritical care can improve outcomes and quality of life of patients who are severely ill, understanding its structure, clinical practice and multimodal neuromonitoring is essential for further development of this field. We present herein the historical evolution of neurocritical care units and their current organization, as well as the spectrum of neurocritical diseases and available modalities for neuromonitoring.

Introduction

Critical care medicine and the concept of intensive care unit is fast 70 years old and was evolved after mechanical ventilation with positive pressure was shown to be a solution for polio victims with respiratory insufficiency[1]. The rapid grow up of the specialty in the following years resulted in the establishment of specialized intensive care units (ICU), such as postoperative neurosurgical units and, later, neuroscience ICUs, which was dedicated to the treatment of critically ill neurological patients[2].

As a continuously evolving subspecialty of intensive care medicine, critical care and management of neurosurgical and neurological patients is a developing concept involving many clinical entities and new technological modalities. Recently, with the rapid development of acute stroke care and endovascular therapy, neurological critical care units (NCCUs) covered further clinical problems, expanding their spectrum of critically ill patients[3].

As the clinical spectrum and therapeutic complexity of critically ill neurological patients admitted to NCCU is continuously evolving, dedicated specialized multidisciplinary teams are required to optimal management of acutely ill patients with life threating neurological problems. In this context, a new subspecialization in neurology has emerged, individuals trained to deal with the complexity of these issues, called neurointensivists. These experts are not only involved in the treatment of primary or secondary neurological problems, they are also dedicated to the development of this field as well as they play a key role in the function of the multidisciplinary team of NCCUs[4],[5].

In this review article, we present the spectrum of neurological patients treated in NCCUs, the existing modalities of neurointensive monitoring, as well as proposed organization and infrastructure of a NCCU.

Historical Evolution of NCCU

Although care of highly complex critically ill patients was always challenging in medicine, progress in this filed was intensified in the second part of 20th century[2]. Currently COVID-19 pandemic triggered further advancement in vaccine development. Similarly, it was poliomyelitis epidemic, which catalyzed the evolution of critical care of patients. Although units for intensive care of postoperative neurosurgical patients were already existed, it was the pandemic, which led to a further development of the concept of intensive care units[6].

In the early 1950s, Lassen and Ibsen, amid the pandemic of a virulent strain of poliomyelitis, utilized manual mechanical ventilation to improve clinical outcome of patients with respiratory failure or bulbar weakness. Emergency tracheostomy and respiratory support with manual bag ventilation (conducted by medical students) simplified care of critically-ill patients and resulted to a mortality drop from 80% to 50%[1],[7]. That led to a further sophistication and improvement of care, practice and technical equipment; a multidisciplinary special ward called intensive care unit was developed and expanded to the majority of large hospitals[8],[9].

Improving technology with advances in mechanical ventilation, monitoring of invasive hemodynamics and incubators for newborns led to the development of more specialized units, such as surgical ICUs, coronary care units, trauma and neonatal ICUs. Evidence was provided suggesting a significant decline in mortality of patients treated with mechanical ventilation in ICUs compared with those in general wards[10], leading to the acceptance and further expansion of this concept. In this aspect, care of traumatic brain injury in specialized ICUs was the initial step for the evolution of neurocritical care[2]. The close cooperation of neurosurgeons and consulting neurologists led to the first neuroscience ICUs, treating both neurosurgical as well as neurological patients with meningitis and status epilepticus[11].

The specialty of critical care and emergency neurology was further developed in following decades focused on stupor and coma as well joined training of neurologists and intensivists and leading positions of neurologists in NCCUs, while acute brain injury and its complications along with recognition and treatment of acute medical and surgical acute neurology was recognized as important additional skill of neurologists[2],[12]. Societies for intensive or neurocritical care, such as the international Neurocritical Care Society or the national Deutsche Gesellschaft für Neurointensiv- und Notfallmedizin were founded, guidelines and special specialization programs were development to sufficiently train and qualify neurologists for neurocritical care [13]-[15]. Currently, NCCUs are mostly units treating neurologic and neurosurgical patients, so that patients could benefit from both expertise in dealing with their complex problems. Future perspectives may include a board certification through neurologic societies. Neurocritical care is expected to expand to other fields of expertise, such as pediatrics with the recognition of a sub-specialized field of pediatric neurocritical care[16], while development in multimodal monitoring requires further research and standardization[17],[18] for the future.

General Organization and Infrastructure

Most modern NCCUs are mixed units treating neurological and neurosurgical patients, functioning either inside a general ICU as dedicated beds or in separate autonomous units. A survey in Germany showed that only 20% of NCCUs functioned as in-

dependent intensive care units of neurology or neurosurgical departments. The majority of neurocritical beds were part of interdisciplinary units, where only 25% of them had a neurologist in their team[19],[20].

The organization of NCCUs is not always clearly defined. An ICU can be open, semi-open and closed. By an open ICU any physician can admit and care for ICU patients, while in a semi-open ICU involves consulting intensivists, while patients are admitted from other physicians. By the closed ICU, which is typical for medical ICUs, intensivists admit and attend all ICU patients[21]. Team composition may vary and can include a large variety of specialists.

Given this lack of organizational criteria for the development of NCCUs, Neurocritical Care Society tried to outline a recommend framework for the structure, personnel and processes for a successful neurocritical care program[22].

Three levels of NCCUs can be defined. Level I units are comprehensive centers of neurocritical care equipped and able to provide expert and interdisciplinary care, featuring a wide spectrum of advanced monitoring and surgical and medical treatment, while offers advanced professional training. Level II units are able to stabilize acutely ill patients and treat stable neurocritical diseases. A Level III unit can evaluate and stabilize neurological emergencies, while facilitates transfer to Level I and II units[22]-[24].

A good coordinated, multidisciplinary team is critical prerequisite for the optimal function of the unit. It has been shown that an interdisciplinary team with expertise in neurocritical care can achieve better outcomes regarding mortality, functional outcomes and resource management [25]-[27]. Standards for continuous training and physician staffing of the interdisciplinary team have been proposed in detail[2][2].

Similarly, adequate nurse training and competency in neurocritical care is required to provide safe and quality care in NCCUs. Skill and competency of the nurses should be assessed periodically using quality indicators describing nursing care[28]. Staffing ratios for an optimal nursing care have been also proposed[22]. Specialty certifications are also an indicator of quality of care and should be encouraged as it may be also associated to improved patients' outcomes[29],[30].

Of interest is the important role of pharmacists as essential members of the interdisciplinary team of the NCCU. Studies suggest that intensive care pharmacists may lead to improvement of care and patients' outcome, due to reduce of adverse drug reactions[31]-[33], decrease ventilator days [34] and improvements in morbidity, mortality and length of stay[35],[36], while there are also evidence suggesting an optimized resource management by reducing medication costs[37].

Furthermore, respiratory therapists applying protocols and procedures regarding mechanical ventilation and tracheostomy[38], as well as physical, occupational and speech therapists and qualified dietitians[39] may improve outcomes and cost-effectiveness as well as successfully evaluate and dealing with the complexity of problems regarding neurocritical care.

Of importance regarding processes and safety in NCCU is the building and implementation of protocols and guidelines combined with the evaluation of outcomes[40]. Safety of patients' care is also an essential part of ICU structure and the quality control of the unit's function. Standardized processes, guidelines, protocols and checklists can help reducing errors and building a culture of safety, which affects patient outcomes. Recurrent evaluation and improvements in quality of neurocritical care as part of the structure of a NCCU is essential for the maintenance of a safe environment for patients and staff[41]-[45].

Multimodal monitoring in NCCU

As most of the patients with severe neurological and neurosurgical diseases in NCCU are sedated and intubated, neurologic examination, although essential for clinical evaluation of the patient, may be extremely difficult and insufficient. Thus, neurocritical monitoring parallel to the monitoring of systemic parameters, such as cardiac rhythm, arterial blood pressure, oxygen saturation, temperature etc. is of essential importance for the implementation and response of the patient to therapeutic interventions, as well as detection of early signs of a neurological decompensation. In addition, neurocritical monitoring may help understanding the complexity of the underlying disorders, detecting an early neurological deterioration, guiding individualized care decisions and implementing therapeutic protocols and eventually improving neurological outcome and quality of life of patients with severe neurological illnesses[46].

Global neurologic status remains a tool to evaluate patients' clinical status and is recommended to be routinely performed. However, a change in neurological status may often present too late to inform therapeutic management. Therefore, various neuromonitoring tools have been development for different physiologic parameters, which can adequately reflect patients' pathology[47].

The concept of multimodal monitoring aims to detect a secondary brain injury and guide therapeutic decisions. Monitor of intracranial pressure (ICP) is a wide spread technique used mainly to detect elevated intracranial pressure and imminent brain herniation in high-risk patients with acute brain trauma and imaging or clinical features suggestive of increased intracranial pressure[48].

Monitor of ICP can be done either through a ventriculostomy or using intraparenchymal monitoring,

as these are the gold standards for measuring ICP. Other invasive methods of ICP monitor exist, however their measurements are less accurate[49]. Alternatively, a noninvasive method to monitor ICP can be used, although there are not very accurate too. Transcranial Doppler can be used to predict ICP, by evaluating various parameters, however accuracy of this method is low[50]. Tympanic membrane displacement is another method based on the transmission of the CNS pressure to the perilymph of cochlea, however this technique is characterized from several limitations[5][1].

Electroencephalography is frequently implemented in NCCUs not only in the context of status epilepticus and for the detection of epileptiform activity in general, but also after cardiac arrest and prediction of cerebral vasospasm after subarachnoidal hemorrhage. As a monitor of cortical function, EEG reactivity and burst suppression musters are markers predicting recovery after a cardiac arrest, while changes in EEG pattern may predict changes in cerebral blood flow in the context of vasospasm after subarachnoid hemorrhage[52].

Transcranial Doppler sonography in neurointensive care can have many applications as an inexpensive and non-invasive method. Monitoring of vasospasm following a subarachnoid hemorrhage can predict the onset of ischemia, as increased systolic flow velocities are related to delayed cerebral ischemia and poor outcomes. Although TCD has been shown to be highly sensitive and offering a negative predictive value for delayed ischemia[53],[54], lack of studies regarding the impact of TCD on clinically relevant outcomes has limited its use. Furthermore, indications for TCD in NCCUs are the detection of microembolic signals due to carotid stenosis, helping estimating the stroke risk, the evaluation of cerebrovascular reserve and the assessment of cerebral autoregulation[55]. Although not typically part of a multimodal neuromonitoring, these TCD applications may inform clinical decision making in NCCUs and lea to improvements in patients' outcomes.

Cerebral microdialysis is a technique involving a catheter inserted in brain parenchyma and allowing frequent sampling and analysis of various markers of interest, such as glucose, glutamate, lactate and pyruvate. Although relative safe, this method has many limitations such as episodic collection of samples and right placement of the probe in the parenchyma. In addition, lack of evidence and trials regarding cerebral microdialysis limits practical interpretation of findings and development of recommended practices[56].

Sensors for brain tissue oxygenation can be implanted to evaluate brain tissue oxygen tension. There is evidence of a correlation between reduced brain tissue oxygenation tension and worse outcome[57]. Monitoring of ICP in combination with measurements of brain tissue oxygenation compared to ICP monitoring alone resulted in a significant decrease of average duration and depth of tissue brain hypoxia and a trend toward lower mortality and favorable outcomes[58]. Further, near-infrared sprectroscopy measures the attenuation of reflected light, which depends on the level of oxygen saturation in blood. Noninvasive sensors can measure brain parenchyma oxygenation, although their use can be limited from factors such as skin tone or scull thickness. Additionally, although there is still a lack of evidence in literature regarding the impact of this modality in patients' outcome, its combined use with other modalities can be implemented in monitoring cerebral autoregulation[59]. Alternatively, jugular venous bulb oximetry is an invasive method less frequently used and is subject to many limitations, such as low accuracy and secondary complications, such as infection and jugular venous thrombosis and should be used only as part of a multimodal monitoring[52].

Finally, regional cerebral flowmetry is a method used to monitor cerebral blood flow. Using a thermal diffusor flowmeter, blood flow can be estimated from thermal loss along two elements. This method has its limitations, as it is highly sensitive to positioning and its accuracy depends on patient temperatures. There is also a lack of evidence regarding its predictive role. Alternatively, a laser doppler flowmeter measures erythrocyte flux directly, however its use is still experimentally[56].

Neurological Diseases and Outcomes

Although initially neurocritical care involved brain injury and neurosurgical patients, it currently involves a broad spectrum of neurological diseases and conditions related to disorders of consciousness, circulatory or respiratory functions as a result of a neurological disease or complications of a neurological disease such as infections, sepsis, aspiration etc. Next to traumatic brain or spine injury, neurologic diseases associated with neurocritical care are acute cerebrovascular disorders, infectious disorders, such as encephalitis or abscesses, or inflammatory disorders, such as NMDAR-encephalitis or severe Guillain-Barre syndrome, refractory status epilepticus or brain tumors. More rarely, disorders associated with neurodegenerative diseases, such as a Parkinson crisis or respiratory insufficiency by ALS, as well as hypoxic or metabolic encephalopathies, tetanus, intoxications or a malignant neuroleptic syndrome may necessitate treatment in NCCUs[60].

There is robust evidence that neurocritical care improves outcomes, especially when specialized neurointensivists are involved[61],[62]. A reduction of length of stay, without increase in complications and increased chances of discharge to home have been related to

more clinician experience due to patient volume, adherence to protocols, earlier catheter removal and mobilization and use of improved technology and neuromonitoring data[61],[63]-[66].

Outcomes of patients with acute cerebrovascular disorders have been improved due to the development of stroke units[67]. Neurocritical care has also been associated to better outcomes of stroke patients. A benefit for patients with ischemic stroke, as well as intracerebral hemorrhage, has been found regarding length of stay, decreased mortality and increased rate of return to pre-stroke function when neurointensivists were involved in patients' treatment. Similarly, improved outcomes have been shown for patients with intracerebral hemorrhage treated in NCCUs [68]-[71]. Regarding subarachnoidal hemorrhage, there is evidence of decreased length of stay in hospital, decreased rate of ventriculoperitoneal shunting, decreased mortality and increased rate of favorable disposition with increased rate of good functional outcome for patients treated in specialized neurocritical units with presence of neurointensivists[72]-[74].

Apart from acute cerebrovascular disorders and traumatic brain injury, data regarding other diseases are scarce in literature and not always consistent due to heterogeneity. In one study patients with status epilepticus admitted to NCCU were more likely to become continuous electroencephalograms and less likely to be intubated compared to patients treated in a medical ICA, however the overall mortality, length of stay and outcome was not different between these two groups[75]. Outcome of cerebral venous sinus thrombosis was improved after institution of NCCU, however data for other diseases are in general rare[21].

In addition, there are evidence of a financial benefit of a NCCU. Although neurocritical illnesses are costly and resource demanding [76], NCCUs staffed with neurointensivists can lead to lower costs due to decrease in length of stay and lower total costs of care[77],[78]. While in another study a dedicated NCCU was related to higher costs, lower mortality and better quality of life outweighed the extra NCCU costs resulting eventually to improved cost-effectiveness[79].

Conclusions

Neurocritical care has been evolved in the last decades and is now an essential part of critical care in many health systems worldwide. The spectrum of neurological illnesses treated in an NCCU has similarly been evolved. There is convincing evidence of improved outcomes of neurocritically ill patients, however functional outcomes remain oft poor. Beside improvements in protocols and training of neurointensivists, technological advances have improved neurocritical monitoring. However, multimodal monitoring needs further research to elucidate its role in informing therapeutic decisions. Patients' outcomes depend on the interpretation of data from multimodal monitoring, implementation of informed protocols regarding patients' management and developing and implementation of therapy according to changes detecting in multimodal monitoring. Neurointensivists and NCCUs with their interdisciplinary teams are expecting to have a leading role not only in treating neurocritically ill patients, but also in research and further scientific advancement of this field.

References

[1] Lassen HC. A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. ***Lancet***. Jan 3 1953;1(6749):37-41. doi:10.1016/s0140-6736(53)92530-6

[2] Wijdicks EF. The history of neurocritical care. ***Handb Clin Neurol***. 2017;140:3-14. doi:10.1016/B978-0-444-63600-3.00001-5

[3] Michalski D, Jungk C, Beynon C, et al. [Focus on neurological intensive care medicine 2022/2023 : Summary of selected intensive medical care studies]. ***Anaesthesiologie***. Dec 2023;72(12):894-906. Fokus Neurologische Intensivmedizin 2022/2023 : Zusammenfassung ausgewahlter intensivmedizinischer Studien. doi:10.1007/s00101-023-01352-7

[4] Ropper AH. Neurological intensive care. ***Ann Neurol***. Oct 1992;32(4):564-9. doi:10.1002/ana.410320413

[5] Smith M. I. Neurocritical care: has it come of age? ***Br J Anaesth***. Dec 2004;93(6):753-5. doi:10.1093/bja/aeh275

[6] Hilberman M. The evolution of intensive care units. ***Crit Care Med***. Jul-Aug 1975;3(4):159-65. doi:10.1097/00003246-197507000-00006

[7] Ibsen B. The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952. ***Proc R Soc Med***. Jan 1954;47(1):72-4.

[8] Bryan-Brown CW. My first 50 years of critical care (1956-2006). ***Am J Crit Care***. Jan 2007;16(1):12-6.

[9] Rosengart MR. Critical care medicine: landmarks and legends. ***Surg Clin North Am***. Dec 2006;86(6):1305-21. doi:10.1016/j.suc.2006.09.004

[10] Rogers RM, Weiler C, Ruppenthal B. Impact of the respiratory intensive care unit on survival of patients with acute respiratory failure. ***Chest***. Jul 1972;62(1):94-7. doi:10.1378/chest.62.1.94

[11] Wijdicks EF, Worden WR, Miers A, Piepgras DG. The early days of the neurosciences intensive care unit. ***Mayo Clin Proc***. Sep 2011;86(9):903-

6. doi:10.4065/mcp.2010.0815
[12] Borel C, Hanley D. Neurologic intensive care unit monitoring. ***Crit Care Clin***. Jul 1985;1(2):223-39.
[13] Smith WS, Weingart S. Emergency Neurological Life Support (ENLS): what to do in the first hour of a neurological emergency. ***Neurocrit Care***. Sep 2012;17 Suppl 1:S1-3. doi:10.1007/s12028-012-9741-x
[14] Diringer MN, Bleck TP, Claude Hemphill J, 3rd, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. ***Neurocrit Care***. Sep 2011;15(2):211-40. doi:10.1007/s12028-011-9605-9
[15] Wijdicks EF. The journal and its first decade. ***Neurocrit Care***. Feb 2014;20(1):1-2. doi:10.1007/s12028-013-9943-x
[16] Murphy SA, Bell MJ, Clark ME, Whalen MJ, Noviski N. Pediatric Neurocritical Care: A Short Survey of Current Perceptions and Practices. ***Neurocrit Care***. Oct 2015;23(2):149-58. doi:10.1007/s12028-015-0120-2
[17] Le Roux P, Menon DK, Citerio G, et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care : a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. ***Intensive Care Med***. Sep 2014;40(9):1189-209. doi:10.1007/s00134-014-3369-6
[18] Bouzat P, Marques-Vidal P, Zerlauth JB, et al. Accuracy of brain multimodal monitoring to detect cerebral hypoperfusion after traumatic brain injury*. ***Crit Care Med***. Feb 2015;43(2):445-52. doi:10.1097/CCM.0000000000000720
[19] Bosel J, Kowoll C, Kahmann J, Dziewas R, Schirotzek I, Dohmen C. [Survey study: update on neurological intensive care in Germany 2012: structure, standards and scores in neurological intensive care units]. ***Nervenarzt***. Dec 2012;83(12):1609-18. Umfragestudie „Update Neurointensiv Deutschland 2012": Struktur, Standards und Scores auf deutschen Neurointensivstationen. doi:10.1007/s00115-012-3541-6
[20] Busse O, Hillmann S, Grond M. [Neurointensive care in Germany : Results of an inspection of intensive care units]. ***Nervenarzt***. Feb 2018;89(2):147-155. Neurointensivmedizin in Deutschland : Ergebnisse einer Begehung von Intensivstationen. doi:10.1007/s00115-017-0446-4
[21] Busl KM, Bleck TP, Varelas PN. Neurocritical Care Outcomes, Research, and Technology: A Review. ***JAMA Neurol***. May 1 2019;76(5):612-618. doi:10.1001/jamaneurol.2018.4407
[22] Moheet AM, Livesay SL, Abdelhak T, et al. Standards for Neurologic Critical Care Units: A Statement for Healthcare Professionals from The Neurocritical Care Society. ***Neurocrit Care***. Oct 2018;29(2):145-160. doi:10.1007/s12028-018-0601-1
[23] Rosenberg DI, Moss MM, American Academy of Pediatrics Section on Critical C, American Academy of Pediatrics Committee on Hospital C. Guidelines and levels of care for pediatric intensive care units. ***Pediatrics***. Oct 2004;114(4):1114-25. doi:10.1542/peds.2004-1599
[24] Marshall JC, Bosco L, Adhikari NK, et al. What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine. ***J Crit Care***. Feb 2017;37:270-276. doi:10.1016/j.jcrc.2016.07.015
[25] Suarez JI, Zaidat OO, Suri MF, et al. Length of stay and mortality in neurocritically ill patients: impact of a specialized neurocritical care team. ***Crit Care Med***. Nov 2004;32(11):2311-7. doi:10.1097/01.ccm.0000146132.29042.4c
[26] Kramer AH, Zygun DA. Do neurocritical care units save lives? Measuring the impact of specialized ICUs. ***Neurocrit Care***. Jun 2011;14(3):329-33. doi:10.1007/s12028-011-9530-y
[27] Lott JP, Iwashyna TJ, Christie JD, Asch DA, Kramer AA, Kahn JM. Critical illness outcomes in specialty versus general intensive care units. ***Am J Respir Crit Care Med***. Apr 15 2009;179(8):676-83. doi:10.1164/rccm.200808-1281OC
[28] Brown DS, Donaldson N, Burnes Bolton L, Aydin CE. Nursing-sensitive benchmarks for hospitals to gauge high-reliability performance. ***J Healthc Qual***. Nov-Dec 2010;32(6):9-17. doi:10.1111/j.1945-1474.2010.00083.x
[29] Fleischman RK, Meyer L, Watson C. Best practices in creating a culture of certification. ***AACN Adv Crit Care***. Jan-Mar 2011;22(1):33-49. doi:10.1097/NCI.0b013e3182062c4e
[30] Leyden C. Certification as a Quality Initiative. ***J Nurs Adm***. Oct 2015;45(10):467-8. doi:10.1097/NNA.0000000000000234
[31] Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. ***JAMA***. Jul 21 1999;282(3):267-70. doi:10.1001/jama.282.3.267
[32] Ng TM, Bell AM, Hong C, et al. Pharmacist monitoring of QTc interval-prolonging medications in critically ill medical patients: a pilot study. ***Ann Pharmacother***. Apr 2008;42(4):475-

82. doi:10.1345/aph.1K458
[33] Rivkin A, Yin H. Evaluation of the role of the critical care pharmacist in identifying and avoiding or minimizing significant drug-drug interactions in medical intensive care patients. ***J Crit Care***. Feb 2011;26(1):104 e1-6. doi:10.1016/j.jcrc.2010.04.014
[34] Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist-enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. ***Crit Care Med***. Feb 2008;36(2):427-33. doi:10.1097/01.CCM.0000300275.63811.B3
[35] MacLaren R, Bond CA, Martin SJ, Fike D. Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections. ***Crit Care Med***. Dec 2008;36(12):3184-9. doi:10.1097/CCM.0b013e31818f2269
[36] Netzer G, Liu X, Shanholtz C, Harris A, Verceles A, Iwashyna TJ. Decreased mortality resulting from a multicomponent intervention in a tertiary care medical intensive care unit. ***Crit Care Med***. Feb 2011;39(2):284-93. doi:10.1097/CCM.0b013e3181ffdd2f
[37] Weant KA, Armitstead JA, Ladha AM, Sasaki-Adams D, Hadar EJ, Ewend MG. Cost effectiveness of a clinical pharmacist on a neurosurgical team. ***Neurosurgery***. Nov 2009;65(5):946-50; discussion 950-1. doi:10.1227/01.NEU.0000347090.22818.35
[38] Kollef MH, Shapiro SD, Silver P, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. ***Crit Care Med***. Apr 1997;25(4):567-74. doi:10.1097/00003246-199704000-00004
[39] Task Force of ASPEN, American Dietetic Association Dietitians in Nutrition Support Dietetic Practice G, Russell M, et al. American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and American Dietetic Association (ADA): standards of practice and standards of professional performance for registered dietitians (generalist, specialty, and advanced) in nutrition support. ***Nutr Clin Pract***. Oct 2007;22(5):558-86. doi:10.1177/0115426507022005558
[40] Stockwell DC, Slonim AD. Quality and safety in the intensive care unit. ***J Intensive Care Med***. Jul-Aug 2006;21(4):199-210. doi:10.1177/0885066606287079
[41] Huang DT, Clermont G, Kong L, et al. Intensive care unit safety culture and outcomes: a US multicenter study. ***Int J Qual Health Care***. Jun 2010;22(3):151-61. doi:10.1093/intqhc/mzq017
[42] Dykes PC, Rozenblum R, Dalal A, et al. Prospective Evaluation of a Multifaceted Intervention to Improve Outcomes in Intensive Care: The Promoting Respect and Ongoing Safety Through Patient Engagement Communication and Technology Study. ***Crit Care Med***. Aug 2017;45(8):e806-e813. doi:10.1097/CCM.0000000000002449
[43] Wick EC, Galante DJ, Hobson DB, et al. Organizational Culture Changes Result in Improvement in Patient-Centered Outcomes: Implementation of an Integrated Recovery Pathway for Surgical Patients. ***J Am Coll Surg***. Sep 2015;221(3):669-77; quiz 785-6. doi:10.1016/j.jamcollsurg.2015.05.008
[44] Pronovost PJ, Weast B, Holzmueller CG, et al. Evaluation of the culture of safety: survey of clinicians and managers in an academic medical center. ***Qual Saf Health Care***. Dec 2003;12(6):405-10. doi:10.1136/qhc.12.6.405
[45] Curtis JR, Cook DJ, Wall RJ, et al. Intensive care unit quality improvement: a "how-to" guide for the interdisciplinary team. ***Crit Care Med***. Jan 2006;34(1):211-8. doi:10.1097/01.ccm.0000190617.76104.ac
[46] Yang MT. Multimodal neurocritical monitoring. ***Biomed J***. Jun 2020;43(3):226-230. doi:10.1016/j.bj.2020.05.005
[47] Peacock SH, Tomlinson AD. Multimodal Neuromonitoring in Neurocritical Care. ***AACN Adv Crit Care***. Summer 2018;29(2):183-194. doi:10.4037/aacnacc2018632
[48] Le Roux P, Menon DK, Citerio G, et al. The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: a list of recommendations and additional conclusions: a statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. ***Neurocrit Care***. Dec 2014;21 Suppl 2(Suppl 2):S282-96. doi:10.1007/s12028-014-0077-6
[49] Eide PK, Sorteberg W. Simultaneous measurements of intracranial pressure parameters in the epidural space and in brain parenchyma in patients with hydrocephalus. ***J Neurosurg***. Dec 2010;113(6):1317-25. doi:10.3171/2010.7.JNS10483
[50] Brain Trauma F, American Association of Neurological S, Congress of Neurological S, et al. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. ***J Neurotrauma***. 2007;24 Suppl 1:S37-44. doi:10.1089/neu.2007.9990
[51] Shimbles S, Dodd C, Banister K, Mendelow AD, Chambers IR. Clinical comparison of tympanic membrane displacement with invasive intracranial pressure measurements. ***Physiol Meas***. Dec 2005;26(6):1085-92. doi:10.1088/0967-

3334/26/6/017
[52] Claassen J, Vespa P, Participants in the International Multi-disciplinary Consensus Conference on Multimodality M. Electrophysiologic monitoring in acute brain injury. ***Neurocrit Care***. Dec 2014;21 Suppl 2:S129-47. doi:10.1007/s12028-014-0022-8
[53] Kumar G, Shahripour RB, Harrigan MR. Vasospasm on transcranial Doppler is predictive of delayed cerebral ischemia in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis. ***J Neurosurg***. May 2016;124(5):1257-64. doi:10.3171/2015.4.JNS15428
[54] Esmael A, Flifel ME, Elmarakby F, Belal T. Predictive value of the transcranial Doppler and mean arterial flow velocity for early detection of cerebral vasospasm in aneurysmal subarachnoid hemorrhage. ***Ultrasound***. Nov 2021;29(4):218-228. doi:10.1177/1742271X20976965
[55] Bonow RH, Young CC, Bass DI, Moore A, Levitt MR. Transcranial Doppler ultrasonography in neurological surgery and neurocritical care. ***Neurosurg Focus***. Dec 1 2019;47(6):E2. doi:10.3171/2019.9.FOCUS19611
[56] Rivera Lara L, Puttgen HA. Multimodality Monitoring in the Neurocritical Care Unit. ***Continuum (Minneap Minn)***. Dec 2018;24(6):1776-1788. doi:10.1212/CON.0000000000000671
[57] Oddo M, Bosel J, Participants in the International Multidisciplinary Consensus Conference on Multimodality M. Monitoring of brain and systemic oxygenation in neurocritical care patients. ***Neurocrit Care***. Dec 2014;21 Suppl 2:S103-20. doi:10.1007/s12028-014-0024-6
[58] Okonkwo DO, Shutter LA, Moore C, et al. Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial. ***Crit Care Med***. Nov 2017;45(11):1907-1914. doi:10.1097/CCM.0000000000002619
[59] Rivera-Lara L, Geocadin R, Zorrilla-Vaca A, et al. Validation of Near-Infrared Spectroscopy for Monitoring Cerebral Autoregulation in Comatose Patients. ***Neurocrit Care***. Dec 2017;27(3):362-369. doi:10.1007/s12028-017-0421
[60] Bosel J. [Modern principles of neurocritical care]. ***Nervenarzt***. Dec 2018;89(12):1411-1427. Moderne Prinzipien der neurologischen Intensivmedizin. doi:10.1007/s00115-018-0634-x
[61] Kramer AH, Zygun DA. Neurocritical care: why does it make a difference? ***Curr Opin Crit Care***. Apr 2014;20(2):174-81. doi:10.1097/MCC.0000000000000076
[62] Finley Caulfield A, Mlynash M, Eyngorn I, et al. Prognostication of ICU Patients by Providers with and without Neurocritical Care Training. ***Neurocrit Care***. Aug 2022;37(1):190-199. doi:10.1007/s12028-022-01467-6
[63] Varelas PN, Conti MM, Spanaki MV, et al. The impact of a neurointensivist-led team on a semiclosed neurosciences intensive care unit. ***Crit Care Med***. Nov 2004;32(11):2191-8. doi:10.1097/01.ccm.0000146131.03578.21
[64] Varelas PN, Hacein-Bey L, Schultz L, Conti M, Spanaki MV, Gennarelli TA. Withdrawal of life support in critically ill neurosurgical patients and in-hospital death after discharge from the neurosurgical intensive care unit. Clinical article. ***J Neurosurg***. Aug 2009;111(2):396-404. doi:10.3171/2009.3.JNS08493
[65] Kramer AH, Zygun DA. Declining mortality in neurocritical care patients: a cohort study in Southern Alberta over eleven years. ***Can J Anaesth***. Oct 2013;60(10):966-75. doi:10.1007/s12630-013-0001-0
[66] Russell D, VorderBruegge M, Burns SM. Effect of an outcomes-managed approach to care of neuroscience patients by acute care nurse practitioners. ***Am J Crit Care***. Jul 2002;11(4):353-62.
[67] Jorgensen HS, Nakayama H, Raaschou HO, Larsen K, Hubbe P, Olsen TS. The effect of a stroke unit: reductions in mortality, discharge rate to nursing home, length of hospital stay, and cost. A community-based study. ***Stroke***. Jul 1995;26(7):1178-82. doi:10.1161/01.str.26.7.1178
[68] Bershad EM, Feen ES, Hernandez OH, Suri MF, Suarez JI. Impact of a specialized neurointensive care team on outcomes of critically ill acute ischemic stroke patients. ***Neurocrit Care***. 2008;9(3):287-92. doi:10.1007/s12028-008-9051-5
[69] Varelas PN, Schultz L, Conti M, Spanaki M, Genarrelli T, Hacein-Bey L. The impact of a neuro-intensivist on patients with stroke admitted to a neurosciences intensive care unit. ***Neurocrit Care***. 2008;9(3):293-9. doi:10.1007/s12028-008-9050-6
[70] Knopf L, Staff I, Gomes J, McCullough L. Impact of a neurointensivist on outcomes in critically ill stroke patients. ***Neurocrit Care***. Feb 2012;16(1):63-71. doi:10.1007/s12028-011-9620-x
[71] Diringer MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. ***Crit Care Med***. Mar 2001;29(3):635-40. doi:10.1097/00003246-200103000-00031
[72] Lerch C, Yonekawa Y, Muroi C, Bjeljac M, Keller E. Specialized neurocritical care, severity grade, and outcome of patients with aneurysmal subarachnoid hemorrhage. ***Neurocrit Care***.

2006;5(2):85-92. doi:10.1385/ncc:5:2:85
[73] Josephson SA, Douglas VC, Lawton MT, English JD, Smith WS, Ko NU. Improvement in intensive care unit outcomes in patients with subarachnoid hemorrhage after initiation of neurointensivist co-management. ***J Neurosurg***. Mar 2010;112(3):626-30. doi:10.3171/2009.8.JNS09441
[74] Egawa S, Hifumi T, Kawakita K, et al. Impact of neurointensivist-managed intensive care unit implementation on patient outcomes after aneurysmal subarachnoid hemorrhage. ***J Crit Care***. Apr 2016;32:52-5. doi:10.1016/j.jcrc.2015.11.008
[75] Varelas PN, Corry J, Rehman M, et al. Management of status epilepticus in neurological versus medical intensive care unit: does it matter? ***Neurocrit Care***. Aug 2013;19(1):4-9. doi:10.1007/s12028-013-9840-3
[76] Raj R, Bendel S, Reinikainen M, et al. Costs, outcome and cost-effectiveness of neurocritical care: a multi-center observational study. ***Crit Care***. Sep 20 2018;22(1):225. doi:10.1186/s13054-018-2151-5
[77] Mirski MA, Chang CW, Cowan R. Impact of a neuroscience intensive care unit on neurosurgical patient outcomes and cost of care: evidence-based support for an intensivist-directed specialty ICU model of care. ***J Neurosurg Anesthesiol***. Apr 2001;13(2):83-92. doi:10.1097/00008506-200104000-00004
[78] Varelas PN, Abdelhak T, Wellwood J, Benczarski D, Elias SB, Rosenblum M. The appointment of neurointensivists is financially beneficial to the employer. ***Neurocrit Care***. Oct 2010;13(2):228-32. doi:10.1007/s12028-010-9371-0
[79] Grieve R, Sadique Z, Gomes M, et al. An evaluation of the clinical and cost-effectiveness of alternative care locations for critically ill adult patients with acute traumatic brain injury. ***Br J Neurosurg***. Aug 2016;30(4):388-96. doi:10.3109/02688697.2016.1161166

RESPIRATORY FAILURE AS THE INITIAL CLINICAL MANIFESTATION OF MYASTHENIA GRAVIS IN THE INTENSIVE CARE UNIT: A CASE REPORT

Dimitrios Mysiris, Polyxeni Stamati, Zisis Tsouris, Antonia Tsika, Antonios Provatas, Styliani Ralli, Vasileios Siokas, Efthimios Dardiotis

Department of Neurology, University Hospital of Larissa, School of Medicine, University of Thessaly, Larissa, Greece;

Abstract

Introduction: Myasthenia gravis is an autoimmune disorder affecting the neuromuscular junction. Regarding pathophysiology, autoantibodies target postsynaptic muscle membrane antigens, causing endplate depletion leading to muscle weakness. The clinical spectrum varies from a purely ocular form to severe general weakness affecting limb, bulbar and respiratory muscles. Myasthenic crisis, a medical emergency resulting from involvement of respiratory muscles, may manifest as the initial clinical presentation of myasthenia gravis.

Case report: Herein, we report a case of a 23-year-old male, who presented to the Emergency Department of the University Hospital of Larissa after a car accident. The patient had mild lung injury, without any neurological symptomatology. During hospitalization the patient manifested acute respiratory failure with hypercapnia leading to cardiac arrest, requiring cardiopulmonary resuscitation. The patient was intubated and admitted to the Intensive Care Unit. Despite clinical and laboratory improvement, patient had elevated carbon dioxide levels, disallowing his weaning from ventilation and oxygen supply. Patient's history revealed episodes of blepharoptosis and muscle fatiguability in the form of difficulty performing physical tasks, while neurological examination showed bulbar symptoms, facial, neck and upper extremities muscle weakness, unraveling a potential Myasthenia Gravis phenotype. Serum immunology study disclosed positive antibodies against muscle specific kinase. The patient was treated with intravenous immunoglobulin (IVIg) and then plasma exchange sessions, leading to clinical improvement.

Conclusion: Myasthenia Gravis should be suspected in case of respiratory failure and inability to wean off mechanical ventilation, especially in young adults. When treating a respiratory failure due to a potential myasthenic crisis, plasma exchange or IVIg should be carefully evaluated as an aggressive and rapid treatment option with good prognosis.

Keywords: Myasthenia Gravis, Myasthenic crisis, plasmapheresis, IVIg, intensive care unit;

ΑΝΑΠΝΕΥΣΤΙΚΗ ΑΝΕΠΑΡΚΕΙΑ ΩΣ ΠΡΩΤΗ ΕΚΔΗΛΩΣΗ ΜΥΑΣΘΕΝΕΙΑΣ GRAVIS ΣΤΗ ΜΟΝΑΔΑ ΕΝΤΑΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ: ΠΑΡΟΥΣΙΑΣΗ ΠΕΡΙΣΤΑΤΙΚΟΥ

Δήμητριος Μυσίρης, Πολυξένη Σταμάτη, Ζήσης Τσούρης, Αντωνία Τσίκα, Αντώνιος Προβατάς, Στυλιανή Ράλλη, Βασίλειος Σιώκας, Ευθύμιος Δαρδιώτης

Νευρολογική Κλινική, Πανεπιστημιακό Νοσοκομείο Λάρισας, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας, Λάρισα, Ελλάδα

Περίληψη

Εισαγωγή: Η μυασθένεια Gravis αποτελεί μια χρόνια αυτοάνοση διαταραχή που επηρεάζει τη νευρομυϊκή σύναψη. Παθοφυσιολογικά, αυτοαντισώματα στοχεύουν αντιγόνα της μετασυναπτικής μυικής μεμβράνης, οδηγώντας σε βλάβη της τελικής κινητικής πλάκας και μυική αδυναμία. Το κλινικό φάσμα των συμπτωμάτων κυμαίνεται από μια μεμονωμένη προσβολή των οφθαλμικών μυών έως σοβαρή γενικευμένη μυϊκή αδυναμία που επηρεάζει τους μύες των άκρων, τους προμηκικούς και αναπνευστικούς μύες. Η μυασθενική κρίση, μια επείγουσα ιατρική κατάσταση στην οποία προσβάλλονται οι αναπνευστικοί μύες, μπορεί να αποτελέσει

αρχικό σύμπτωμα της μυασθένειας Gravis.
Περιγραφή περιστατικού: Το περιστατικό που περιγράφεται αφορά άνδρα ηλικίας 23 ετών, που παρουσιάστηκε στο νοσοκομείο μετά από τροχαίο ατύχημα. Ο ασθενής εμφάνισε σημεία ήπιας θλάσης πνευμονικού παρεγχύματος, χωρίς νευρολογική σημειολογία. Κατά τη διάρκεια της νοσηλείας του ο ασθενής παρουσίασε αναπνευστική ανεπάρκεια με υπερκαπνία που οδήγησε σε καρδιοαναπνευστική ανακοπή, όπου και απαιτήθηκε καρδιοαναπνευστική αναζωογόνηση. Ο ασθενής διασωληνώθηκε και εισήχθη στην Μονάδα Εντατικής Θεραπείας. Παρά την κλινική και εργαστηριακή βελτίωση, τα αυξημένα επίπεδα CO2 του ασθενούς εμπόδισαν τον απογαλακτισμό του από τον επεμβατικό αερισμό και την παροχή οξυγόνου. Το ιστορικό του ασθενούς αποκάλυψε επεισόδια βλεφαρόπτωσης και κοπωσιμότητα των μυών με τη μορφή δυσχέρειας στην επιτέλεση καθημερινών δραστηριοτήτων, ενώ η νευρολογική εξέταση ανέδειξε προμηκικά συμπτώματα, μυϊκή αδυναμία προσωπικών μυών , μυών του αυχένα και των άνω άκρων, αποκαλύπτοντας έναν πιθανό φαινότυπο Myasthenia Gravis. Από τον εργαστηριακό έλεγχο ανιχνεύθηκαν αντισώματα κατά της ειδικής μυικής κινάσης. Ο ασθενής έλαβε θεραπεία με ενδοφλέβια γ-σφαιρίνη και έπειτα συνεδρίες πλασμαφαίρεσης , οδηγώντας σε κλινική βελτίωση.
Συμπέρασμα: Το περιστατικό αυτό αναδύει την αναπνευστική ανεπάρκεια και την αδυναμία απογαλακτισμού από το μηχανικό αερισμό, ειδικά σε νεαρούς ενήλικες, ως μια αρχική εκδήλωση της Μυασθένειας Gravis, ειδικά της υποομάδας με αντισώματα έναντι της μυικής ειδικής κινάσης. Κατά τη θεραπεία αναπνευστικής ανεπάρκειας πιθανόν στα πλαίσια μυασθενικής κρίσης, η χορήγηση ενδοφλέβιας γ-σφαιρίνης ή η πλασμαφαίρεση θα πρέπει να αξιολογείται προσεκτικά ως μια επιθετική και ταχεία θεραπευτική επιλογή με καλή πρόγνωση.

Λέξεις ευρετηρίου: Μυασθένεια Gravis; μυασθενική κρίση; πλασμαφαίρεση; μονάδα εντατικής θεραπείας;

Introduction

Myasthenia gravis (MG) is the most common disorder impacting the neuromuscular junction (NMJ) of the skeletal muscles. The cardinal symptoms of MG are muscle weakness and fatigue, predominantly impacting face, neck, eyes, lower and upper limbs muscles [1]. Autoantibodies attack against specific postsynaptic membrane proteins, resulting to electrical impulse transmission reduction across the NMJ, which subsequently generates MG clinical phenomenology [2]. Nicotinic acetylcholine receptors (n-AChRs), muscle-specific kinase (MuSK), lipoprotein-related protein 4 (LRP4), are the main NMJ-related proteins involved as autoantibodies targets in the realm of MG. Myasthenic crisis is a life-threatening and potentially fatal MG exacerbation, characterized by weakness worsening, necessitating intubation or noninvasive ventilation [3]. Although respiratory muscle involvement resulting to respiratory failure, signs of bulbar muscle weakness frequently coexist or may even be the main clinical symptoms in myasthenic crisis course [4]. Here we report a case of respiratory failure due to MuSK-MG, newly diagnosed in intensive care unit, as a result of patient's hypercapnia and inability to wean off ventilation. Written informed consent for the publication of the case report was given by the patient. Detailed information is available on reasonable request from the corresponding author.

Case report

A 23 years old male adult, without any notable medical or family history presented to the hospital after a car accident. Patient's vital signs were stable, the level of consciousness was excellent (Glascow Coma Scale (GCS)=15/15), while laboratory findings revealed a low elevation of carbon dioxide levels (pCO_2=47 mmHg and pH=7.34). A full body computer tomography (CT) was performed revealing a mild lung injury. Consequently, the patient was admitted to cardiothoracic unit. After a couple of hours, the patient was unconsciousness (GCS=7) and manifested cardiac arrest, necessitating cardiopulmonary resuscitation and intensive care unit (ICU) admission for further evaluation and monitoring. Her vital signs revealed hypoxia (pO_2=55 mmHg and SpO_2=82%) and high levels of Carbon dioxide (pCO_2=78 mmHg). As such, mechanical ventilation was applied. A second urgent full body CT was conducted without revealing any further radiological deterioration and after 3 days the patient was awake, but oxygen supply and noninvasive ventilation were still required because of hypercapnia episodes. A neurological examination revealed diminished gag reflex, mild bilateral facial muscle weakness, drop head and proximal muscular weakness in upper extremities, with preserved tendon reflexes and without pyramidal signs, spasticity, and sensory impairment. A brain MRI was performed with unremarkable findings (figure 1). Serum antibodies against AChR, LRP4, Titin and P/Q VGCC were negative, while serum immunology analysis showing positive IgG antibodies against MusSK. The patient was initially treated with intravenous immunoglobulin (2g/kg) and then due to minor clinical improvement, 7 plasma exchange

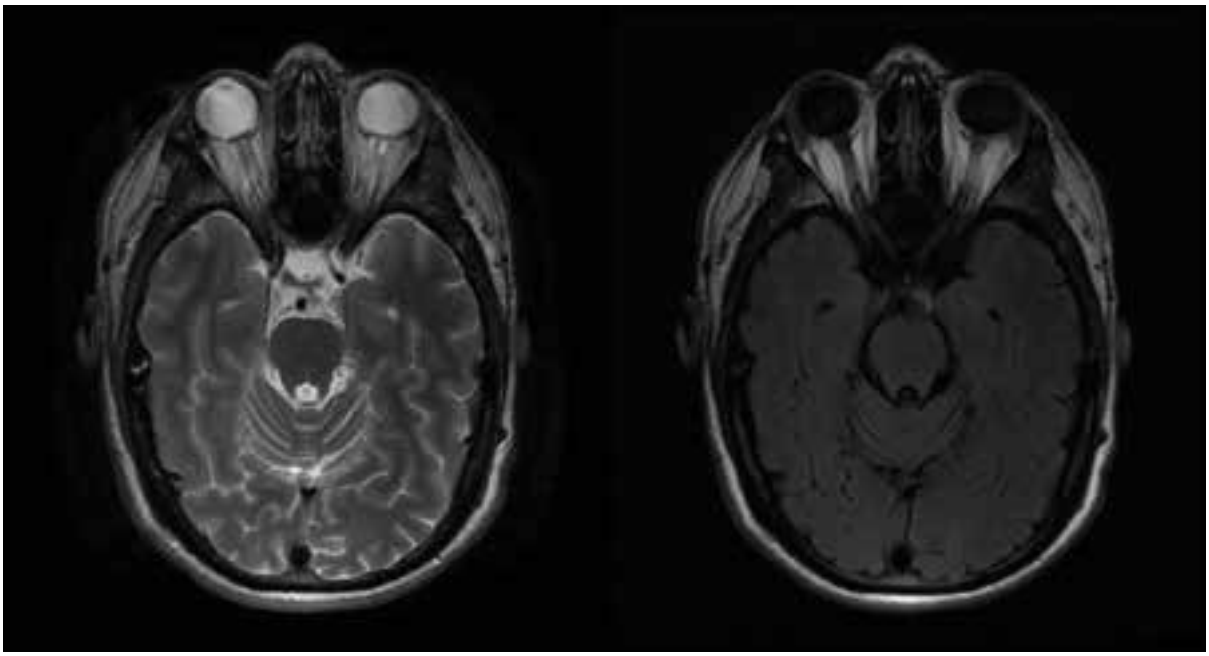


Figure 1: Brain MRI with unremarkable findings in T2 (left) and FLAIR T2 (right) sequences.

sessions were performed. Gradually the patient's muscle strength was increased, and he was able to wean off noninvasive mechanical ventilation and oxygen supply. Prednisolone (50mg) was added in treatment in order to maintain the clinical outcome and the patient discharged at home after 30 days of hospitalization with minimal neurological deficit (mild facial muscle weakness). During the 2-month follow-up the neurological examination was unremarkable without clinical signs indicative MG.

DISCUSSION

Muscle specific kinase is a membrane protein, which orchestrates AChR clustering in NMJ. Specifically, Agrin-LRP4 unit triggers MuSK phosphorylation and in turn a downstream signaling pathway is activated, resulting to the clustering of AChR and signal transduction in muscle endplate level. MuSK-MG accounts for about 5-8% of all MG cases, while antibodies against MuSK presented to approximately 40% of patients with generalized MG who are seronegative for AChR antibodies (Abs) [5]. Compared to AChR-positive MG, MuSK-MG has a different clinical, serological, and therapeutical pattern. Immunologically, MuSK Abs are not potent activators of complement and cell-mediated cytotoxicity, primarily belonging to IgG4 subclass, explaining the long-lasting efficacy of B-cell depletion treatment [6]. Moreover, MuSK Abs titers have been associated with disease severity and less favorable outcome in myasthenic crisis [4]. AChR and MuSK antibodies seropositivity has seldom been observed, reinforcing that these MG-subtypes considered to be distinct entities [2,7].

Regarding of clinical status, MuSK-MG predominantly affects young adults and craniobulbar muscular weakness appears to be more prominent neurological sequelae than AChR- MG. Moreover, acute onset and aggressive disease progression , an increased tendency for myasthenic crisis development, the rare participation of thymus gland with either thymoma or hyperplasia, limited response to cholinesterase inhibitors and worse long-term outcome are all strong indicators of MuSK-MG [5,8,9]. More than 40% of patients experienced bulbar weakness, typically combined with neck and respiratory muscles dysfunction [10]. In MuSK-MG cases drop head due to neck extensor weakness constitutes a crucial neurological symptom, whereas AChR-MG individuals exhibit neck flexor involvement. Compared to AChR-MG, limb weakness is typically milder and less common [11]. Furthermore, despite high doses of immunosuppression, MuSK-MG associated spontaneous exacerbations and myasthenic crises are common [12]. Approximately 10–15% of MuSK- MG patients have a refractory disease or experience disease relapses when their immunosuppressive treatment being tapered, highlighting the importance of aggressive treatment.

Myasthenic crisis constitutes a detrimental condition affecting 15% to 20% of MG patients at least once in their lives. The median period from clinical MG onset to the first myasthenic crisis appearance varies between 8 to 12 months, and myasthenic crisis may be the initial manifestation of MG in 20% of patients [13]. Patients requiring endotracheal in-

tubation during myasthenic crises, hospitalized for an average of 17 days, with 18% necessitating rehabilitation center. The most common trigger factors of a myasthenic crisis are mainly infections and subsequently exposure to temperature extremes, trauma, several medications, surgeries, sleep deprivation, biological stress and roughly one-third to one-half of MG cases have no clear precipitating factor suspected to myasthenic crisis [14]. The goal standard treatment of myasthenic crisis is to secure the airway, quickly initiation of rapid immunomodulatory and immunosuppressive therapy, and to treat as soon as possible identified trigger factors [14,15]. Management of myasthenic crisis includes acute causal treatment by immunoadsorption/plasmapheresis or alternatively with intravenous immunoglobulins. Although both treatment options seem to have equal impact on myasthenic crisis management, progression and long-term effect, a recent systematic review and meta-analysis demonstrated, statistically not significant, that plasmapheresis may have a faster beneficial effect on myasthenia crisis prevention, when compared to IVIG therapy [16].

Conclusion

This case-report proposes respiratory failure as a primary manifestation of MuSK-MG in a young male adult. The involvement of respiratory muscles may combine with cranial and bulbar muscle weakness. In conclusion, given the great heterogeneity of clinical manifestations of MuSK-MG, this case highlights the need for MuSK-Abs testing in patients with unexplained hypercapnia or respiratory failure, especially in cases without an underlying pulmonary disease.

References

[1] Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. ***Nature Reviews Disease Primers***. 2019/05/02 2019;5(1):30. doi:10.1038/s41572-019-0079-y

[2] Dresser L, Wlodarski R, Rezania K, Soliven B. Myasthenia Gravis: Epidemiology, Pathophysiology and Clinical Manifestations. ***J Clin Med***. May 21 2021;10(11)doi:10.3390/jcm10112235

[3] Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. ***Neurology***. Jul 26 2016;87(4):419-25. doi:10.1212/WNL.0000000000002790

[4] Konig N, Stetefeld HR, Dohmen C, et al. MuSK-antibodies are associated with worse outcome in myasthenic crisis requiring mechanical ventilation. ***J Neurol***. Dec 2021;268(12):4824-4833. doi:10.1007/s00415-021-10603-9

[5] Rodolico C, Bonanno C, Toscano A, Vita G. MuSK-Associated Myasthenia Gravis: Clinical Features and Management. ***Front Neurol***. 2020;11:660. doi:10.3389/fneur.2020.00660

[6] Guptill JT, Sanders DB, Evoli A. Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts. ***Muscle Nerve***. Jul 2011;44(1):36-40. doi:10.1002/mus.22006

[7] Huijbers MG, Zhang W, Klooster R, et al. MuSK IgG4 autoantibodies cause myasthenia gravis by inhibiting binding between MuSK and Lrp4. ***Proc Natl Acad Sci U S A***. Dec 17 2013;110(51):20783-8. doi:10.1073/pnas.1313944110

[8] Evoli A, Alboini PE, Damato V, et al. Myasthenia gravis with antibodies to MuSK: an update. ***Ann N Y Acad Sci***. Jan 2018;1412(1):82-89. doi:10.1111/nyas.13518

[9] Lauriola L, Ranelletti F, Maggiano N, et al. Thymus changes in anti-MuSK-positive and -negative myasthenia gravis. ***Neurology***. Feb 8 2005;64(3):536-8. doi:10.1212/01.WNL.0000150587.71497.B6

[10] Pasnoor M, Wolfe GI, Nations S, et al. Clinical findings in MuSK-antibody positive myasthenia gravis: a U.S. experience. ***Muscle Nerve***. Mar 2010;41(3):370-4. doi:10.1002/mus.21533

[11] Evoli A, Tonali PA, Padua L, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. ***Brain***. Oct 2003;126(Pt 10):2304-11. doi:10.1093/brain/awg223

[12] Huang Q, Li F, Zhao S. Spotlight on MuSK positive myasthenia gravis: clinical characteristics, treatment and outcomes. ***BMC Neurol***. Mar 4 2022;22(1):73. doi:10.1186/s12883-022-02593-6

[13] O'Riordan JI, Miller DH, Mottershead JP, Hirsch NP, Howard RS. The management and outcome of patients with myasthenia gravis treated acutely in a neurological intensive care unit. ***Eur J Neurol***. Mar 1998;5(2):137-142. doi:10.1046/j.1468-1331.1998.520137.x

[14] Wendell LC, Levine JM. Myasthenic crisis. ***Neurohospitalist***. Jan 2011;1(1):16-22. doi:10.1177/1941875210382918

[15] Neumann B, Angstwurm K, Mergenthaler P, et al. Myasthenic crisis demanding mechanical ventilation: A multicenter analysis of 250 cases. ***Neurology***. Jan 21 2020;94(3):e299-e313. doi:10.1212/WNL.0000000000008688

[16] Pavlekovics M, Engh MA, Lugosi K, et al. Plasma Exchange versus Intravenous Immunoglobulin in Worsening Myasthenia Gravis: A Systematic Review and Meta-Analysis with Special Attention to Faster Relapse Control. ***Biomedicines***. Nov 29 2023;11(12)doi:10.3390/biomedicines11123180

A YOUNG FEMALE PATIENT WITH MOG ANTIBODY-ASSOCIATED DISEASE AND CLINICAL AND RADIOLOGICAL DISEASE PROGRESSION: A CASE REPORT

Zisis Tsouris, Polyxeni Stamati, Antonios Provatas, Evagelos Sakalakis, Antonia Tsika, Vana Tsimourtou, Vasileios Siokas, Efthimios Dardiotis

Department of Neurology, University Hospital of Larissa, School of Medicine, University of Thessaly, Larissa, Greece;

Abstract

Introduction: Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is an immune-mediated demyelinating disease of the central nervous system. The development of newer cell-based assays for the detection of MOG antibodies further elucidates the highly heterogenous MOGAD phenotype. Furthermore, disease progression independent of relapses is uncommon among MOGAD patients compared to multiple sclerosis (MS) patients.

Case report: Here we present a case of a female patient with MOGAD manifesting recurrent episodes of seizures, neurological deficits, and evidence of clinical and imaging deterioration regardless of disease relapses.

Conclusion: Our case comes to add to the growing clinical phenotype of the disease as well as to highlight the need to further investigate the incidence of relapse-free progression of the disease.

Key words: MOGAD, progression, demyelinating diseases, multiple sclerosis

ΓΥΝΑΙΚΑ ΜΕ ΝΟΣΟ ΣΧΕΤΙΖΟΜΕΝΗ ΜΕ ΑΝΤΙΣΩΜΑΤΑ ΕΝΑΝΤΙ ΤΗΣ MOG ΚΑΙ ΚΛΙΝΙΚΗ ΚΑΙ ΑΠΕΙΚΟΝΙΣΤΙΚΗ ΠΡΟΟΔΟ ΤΗΣ ΝΟΣΟΥ: ΠΑΡΟΥΣΙΑΣΗ ΠΕΡΙΣΤΑΤΙΚΟΥ

Ζήσης Τσούρης, Πολυξένη Σταμάτη, Αντώνιος Προβατάς, Ευάγγελος Σακαλάκης, Αντωνία Τσίκα, Βάνα Τσιμούρτου, Βασίλειος Σιώκας, Ευθύμιος Δαρδιώτης

Department of Neurology, University Hospital of Larissa, School of Medicine, University of Thessaly, Larissa, Greece;

Περίληψη

Εισαγωγή: Η σχετιζόμενη με τα αντισώματα έναντι της γλυκοπρωτεΐνης της μυελίνης των ολιγοδενδροκυττάρων (MOG) νόσος (MOGAD) είναι μια ανοσο-μεσολαβούμενη απομυελινωτική νόσος του κεντρικού νευρικού συστήματος. Η ανάπτυξη νεότερων κυτταρικών δοκιμασιών για την ανίχνευση αντισωμάτων έναντι της MOG κάνει πιο κατανοητό τον ετερογενή φαινότυπο της MOGAD. Επιπλέον, η πρόοδος της νόσου ανεξάρτητα των υποτροπών της είναι μάλλον ασυνήθιστη στους ασθενείς με MOGAD σε σύγκριση με τους ασθενείς με πολλαπλή σκλήρυνση.

Περιγραφή περιστατικού: Το περιστατικό που περιγράφεται αφορά γυναίκα 49 ετών με MOGAD που εμφανίζει επεισόδια επιληπτικών κρίσεων και νευρολογικών ελλειμάτων καθώς και ενδείξεις κλινικής και απεικονιστικής επιδείνωσης ανεξάρτητα από υποτροπές της νόσου.

Συμπέρασμα: Η περίπτωσή μας έρχεται να προσθέσει στον καθορισμό του ετερογενούς κλινικού φαινοτύπου της νόσου καθώς και να αναδείξει την ανάγκη περαιτέρω διερεύνησης της συχνότητας εμφάνισης της προόδου της νόσου μεταξύ των υποτροπών.

Λέξεις ευρετηρίου: MOGAD, προοδευτικότητα, απομυελινωτικά νοσήματα, Πολλαπλή Σκλήρυνση, εγκεφαλίτιδα

Introduction

Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) is an immune-mediated demyelinating disease of the central nervous system (CNS). MOG protein forms only a small part of the outer surface of CNS myelin [1]. It took approximately 40 years from the discovery of MOG antibodies to further understand their role in the pathogenesis of MOGAD [2]. In 2007, antibodies against MOG were first associated with a distinct demyelinating syndrome [3]. Recently, the development of newer cell-based assays for the detection of antibodies against MOG further elucidate the phenotype of MOGAD which includes episodes of optic neuritis, acute disseminated encephalomyelitis (ADEM), transverse myelitis, as well as a combination of neurological deficits due to single or multiple lesions of the brain, brainstem and cerebellum [4-6].

As a demyelinating disease of the CNS, MOGAD has some features that distinguish it from multiple sclerosis (MS) and aquaporin-4 (AQP4)-positive neuromyelitis optica spectrum disease (NMOSD)[7]. Epidemiologically, disease affects people of all ages with a preference in children and with equal preference to both sexes, and an overall prevalence of 20 cases per million [8]. ADEM is most frequent in childhood, while in adulthood the most frequent manifestation is that of optic neuritis [9,10]. Unlike relapsing MS and relapsing episodes of AQP4-positive NMOSD, MOGAD can be either monophasic or relapsing [11,1[2]. The ever-increasing availability of MOG antibody testing and its better clinical documentation leads to new disease phenotypes with manifestations such as seizures, headache, fever, aphasia, and stroke-like episodes, even manifestations from the peripheral nervous system [13,14]. In addition, histopathological and radiological features can further differentiate MOGAD from MS and AQP4-positive NMOSD [9].

Disease progression independent of relapses (PIRA) is a new clinical outcome measure in patients with MS, and it represents the continuous worsening of disability between disease relapses [15]. While in MS, progression is subject of extensive research, in MOGAD there are limited data on its progression between relapses [16]. According to recent data, PIRA is not common among MOGAD patients [17]. Here we present a case of a female patient with MOGAD manifesting recurrent episodes of seizures and neurological deficits and evidence of clinical and imaging deterioration regardless of disease relapses. Written informed consent was obtained by the patient. Detailed information is available upon request.

Case report

A 49-year-old female with a history of peripheral facial nerve palsy, meningitis, iron deficiency anemia, hypothyroidism in early adulthood, and a diagnosis of multiple sclerosis since the age of 36, was referred to the Neurological Department of the University Hospital of Larissa, from a secondary district hospital, where she was admitted, twice in a four-month period, due to acute onset aphasia and right pyramidal weakness after focal to bilateral tonic-clonic seizures. The patient has been receiving disease-modifying treatment with glatiramer acetate since the age of 45. From the family history, a sister with multiple sclerosis is reported. In each of the episodes, thrombolysis with intravenous alteplase, was performed, with resolution of symptoms, followed by systematic treatment with levetiracetam, clopidogrel, and atorvastatin. In our department, magnetic resonance imaging (MRI) of the brain revealed high signal in T2 and diffusion weighted imaging (DWI) sequences in the left hippocampal cortex, extensive leukoencephalopathy, and few contrast-enhanced lesions in the left frontoparietal white matter (**Figure 1A-C**). During her stay, the patient remained free of symptoms and underwent extensive blood and cerebrovascular risk factor examination with no abnormal findings, and she was discharged with treatment.

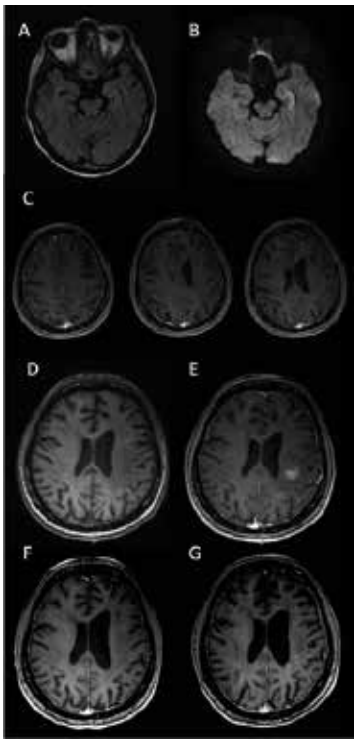
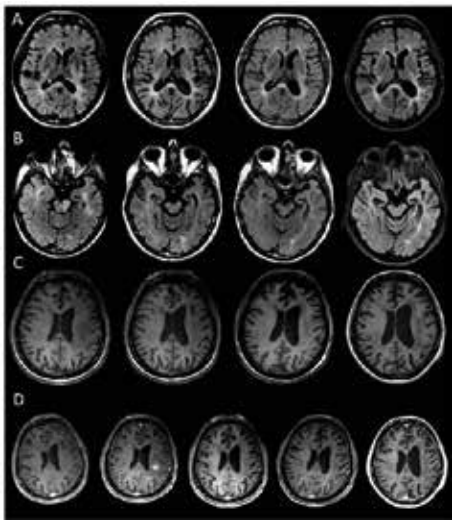


Figure 1. Brain MRI at first admission revealing high signal in axial T2 FLAIR (A) and DWI (B) sequencies in the left hippocampal cortex, and few contrast-enhanced lesions in the left frontoparietal white matter in axial T1 with contrast sequence (C). Second admission brain MRI revealing an increase in the enhancing lesions of the frontoparietal white matter in T1

sequencies without (D) and with (E) contrast. Two months after the last relapse brain MRI on remission with T1 sequence showing no enhancing lesions (F) and 4 months later brain MRI revealing new enhancing lesions in T1 sequence with contrast (G).

After an asymptomatic two-month period, the patient was re-admitted to our department due to subacute onset of aphasia and right limb weakness. The new brain MRI scan revealed increase of the enhancing lesions of the frontoparietal white matter (**Figure 1D-E**).Routine blood tests showed no remarkable abnormalities, while serological studies with autoimmune markers, were not suggestive of autoimmune diseases or recent infections. Cerebrospinal fluid (CSF) analysis showed 2 cells/mm[3], elevated protein (66 mg/dL) and normal glucose (50 mg/dL) levels. In addition, CSF analysis with PCR for several viral, including John Cunningham virus (JCV), and bacterial infections was negative. CSF and serum testing for neuronal antibodies did not yield any positive result. Screening with computed tomography scan of chest and abdomen, whole-body positron emission tomography, and CSF flow cytometric immunophenotyping did not reveal signs of either neoplasia or inflammatory disease. However, further analysis revealed identical oligoclonal bands in CSF and serum, and the absence of serum aquaporin-4 antibodies, while there was a clear positive result (1/1000) by fixed cell-based assay (CBA) of antibodies against MOG. Thus, the diagnosis of



MOGAD was set.

Figure 2. Consecutive brain MRI scans of the patient during relapses and remission periods revealing the accumulation of elevated T2 signal lesions and brain atrophy in T2 FLAIR (A and B) and T1 without contrast (C) sequences, respectively. Sequential brain MRIs highlighting various enhancing lesions on T1 contrast-enhanced sequence (D) during relapses consistent with increase of brain atrophy.

Based on the above diagnosis, the patient was treated with 1000 mg of intravenous (IV) methylprednisolone for 5 days followed by treatment with oral prednisolone (40mg/day). The patient subsequently showed a gradual improvement in symptoms, while immunosuppressive treatment with rituximab was initiated. Six months later and while the patient remained in a clinical and radiological remission (**Figure 1F**), she experienced a recurrence of symptoms, as well as of the enhancing lesions in brain MRI (**Figure 1G**), and the immunosuppressive treatment was switched to mycophenolate mofetil (MMF). During the next 8-month follow-up period, the patient showed recurrence of epileptic episodes, thus lamotrigine was added to her treatment. Further evaluation revealed a decline in cognitive functions, with an Addenbrooke's cognitive examination-revised (ACE-R) scale score of 30/100, and brain atrophy with no enhancing lesions on the consecutive MRIs (**Figure 2A-D**), despite her otherwise stable neurological condition.

Discussion

Clinical phenotypes of MOGAD are highly heterogenous. The development of new methods for detecting MOG antibodies has made it possible to better identify the phenotypes of the disease, with a spectrum of clinical manifestations being constantly added [8]. Overall, optic neuritis is the most common clinical manifestation of the disease, while the disease is more common among children [8]. In children, ADEM is more frequent followed by optic neuritis, while optic neuritis and transverse myelitis are more common among adults [11]. In addition to the well-documented phenotypes, several other clinical manifestations have been reported, such as neurological deficits due to brain, brainstem, and cerebellar lesions, as well as more severe manifestations such as seizures, headache, fever, aphasia and stroke-like episodes as well as encephalopathy [13]. A recently recognized phenotype is cerebral cortical encephalitis which in a recent retrospective study appears to be a disease phenotype in up to 6.7% of MOGAD patients, while its most prominent clinical manifestations include headache, seizures, and encephalopathy [13]. Additionally, data from a prospective MRI study show the predominance of cortical lesions and the presence of leptomeningeal contrast enhancement in patients with MOGAD [18], these findings are consistent with the increased histopathological prevalence of intracortical lesions in patients' brain biopsies [19]. Finally, despite the fact that MOGAD is traditionally a CNS disease, cases of cranial nerve involvement with or without CNS

involvement have been reported [14],[20], while there is also a report of combined central and peripheral demyelination [21].

The clinical course of the disease can be either monophasic or relapsing. There is usually a subacute onset of symptoms over a period of days with varying degrees of recovery of deficits over the following weeks or months [12]. Episodes may be preceded by an infection or vaccination. Approximately 40-50% of MOGAD patients, will have a single episode without any new relapse, while others will have long intervals between relapses [22]. PIRA is a new clinical outcome measure in MS patients, however the accumulation of disability in both MOGAD and AQP4-positive NMOSD patients is widely accepted to be primarily due to relapses of the disease [15]. In a recent retrospective study, only a small percentage of MOGAD patients, with a median(IQR) follow-up of 25.5 (22–36) months, experienced disease progression during relapse-free periods, while the annual PIRA rate was significantly lower than in MS patients [17]. Only 5.5% of MOGAD patients had new T2 or contrast-enhanced lesions revealed on brain MRI during remission period compared to MS patients [1][7]. Regarding brain atrophy, there are even fewer studies in patients with MOGAD. A cohort study revealed significant volumetric changes among MOGAD patients as early as in the first year from the disease onset, while deep gray matter atrophy was observed in all patients, and especially in those with relapsing phenotype [23].

We report a MOGAD patient with a rather rare clinical phenotype, and signs of disease progression between relapses. From patient's medical history, she has been previously diagnosed with MS in the context of relapsing sensory deficits and T2 lesions of deep white matter on brain MRI, however no serum testing for MOG antibodies had been performed due to lack of availability. Although the frequency of MOG antibodies among MS patients is approximately 0.3-2.5% [24], they are usually detected in low titres [25], in contrast to the high titres (1/1000) that our patient had. Our case further contributes to the study of relapse-free progression in MOGAD, as our patient exhibited cognitive decline between the attacks and radiological deterioration with accumulation of deep white matter T2 lesions and brain atrophy on consecutive brain MRIs on relapses and in-between.

Conclusions

Our case comes to add to the growing phenotypes of the disease and to highlight the need to further elucidate the incidence of progression of the disease between episodes. The better understanding of the MOGAD clinical phenotype as well as further research of prognostic markers of the disease could guide clinical decision making in long-term immunosuppressive treatment initiation when necessary.

References

[1] Fujihara K, Sato DK, Nakashima I, et al. Myelin oligodendrocyte glycoprotein immunoglobulin G-associated disease: An overview. ***Clinical and Experimental Neuroimmunology***. 2018;9(S1):48-55. doi:https://doi.org/10.1111/cen3.12434

[2] Linington C, Bradl M, Lassmann H, Brunner C, Vass K. Augmentation of demyelination in rat acute allergic encephalomyelitis by circulating mouse monoclonal antibodies directed against a myelin/oligodendrocyte glycoprotein. ***Am J Pathol***. Mar 1988;130(3):443-54.

[3] O'Connor KC, McLaughlin KA, De Jager PL, et al. Self-antigen tetramers discriminate between myelin autoantibodies to native or denatured protein. ***Nat Med***. Feb 2007;13(2):211-7. doi:10.1038/nm1488

[4] Banwell B, Bennett JL, Marignier R, et al. Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. ***Lancet Neurol***. Mar 2023;22(3):268-282. doi:10.1016/S1474-4422(22)00431-8

[5] Waters PJ, Komorowski L, Woodhall M, et al. A multicenter comparison of MOG-IgG cell-based assays. ***Neurology***. Mar 12 2019;92(11):e1250-e1255. doi:10.1212/WNL.0000000000007096

[6] Tsouris Z, Provatas A, Bakirtzis C, et al. Anti-MOG Positive Bilateral Optic Neuritis and Brainstem Encephalitis Secondary to COVID-19 Infection: A Case Report. ***Neurol Int***. Nov 30 2022;14(4):991-996. doi:10.3390/neurolint14040078

[7] Tsouris Z, Dastamani M, Siokas V, et al. Recurrent episodes of syncope requiring pacemaker implantation as an initial presentation of neuromyelitis optica spectrum disorder. ***Mult Scler Relat Disord***. Oct 2020;45:102423. doi:10.1016/j.msard.2020.102423

[8] de Mol CL, Wong Y, van Pelt ED, et al. The clinical spectrum and incidence of anti-MOG-associated acquired demyelinating syndromes in children and adults. ***Mult Scler***. Jun 2020;26(7):806-814. doi:10.1177/1352458519845112

[9] Sechi E, Cacciaguerra L, Chen JJ, et al. Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD): A Review of Clinical and MRI Features, Diagnosis, and Management. ***Front Neurol***. 2022;13:885218. doi:10.3389/fneur.2022.885218

[10] Waters P, Fadda G, Woodhall M, et al. Serial

Anti-Myelin Oligodendrocyte Glycoprotein Antibody Analyses and Outcomes in Children With Demyelinating Syndromes. ***JAMA Neurol***. Jan 1 2020;77(1):82-93. doi:10.1001/jamaneurol.2019.2940

[11] Cobo-Calvo A, Ruiz A, Maillart E, et al. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: The MOGADOR study. ***Neurology***. May 22 2018;90(21):e1858-e1869. doi:10.1212/WNL.0000000000005560

[12] Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. ***Brain***. Dec 1 2017;140(12):3128-3138. doi:10.1093/brain/awx276

[13] Valencia-Sanchez C, Guo Y, Krecke KN, et al. Cerebral Cortical Encephalitis in Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. ***Ann Neurol***. Feb 2023;93(2):297-302. doi:10.1002/ana.26549

[14] Kyriakaki G, Prattos T, Gkougka D, et al. Abducens nerve mononeuritis as a manifestation of pediatric myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD): a case report. ***Archives of Clinical Neurology***. Nov 2023;32(5)

[15] Lublin FD, Haring DA, Ganjgahi H, et al. How patients with multiple sclerosis acquire disability. ***Brain***. Sep 14 2022;145(9):3147-3161. doi:10.1093/brain/awac016

[16] Molazadeh N, Filippatou AG, Vasileiou ES, Levy M, Sotirchos ES. Evidence for and against subclinical disease activity and progressive disease in MOG antibody disease and neuromyelitis optica spectrum disorder. ***J Neuroimmunol***. Nov 15 2021;360:577702. doi:10.1016/j.jneuroim.2021.577702

[17] Molazadeh N, Akaishi T, Bose G, Nishiyama S, Chitnis T, Levy M. Progression independent of relapses in aquaporin4-IgG-seropositive neuromyelitis optica spectrum disorder, myelin oligodendrocyte glycoprotein antibody-associated disease, and multiple sclerosis. ***Mult Scler Relat Disord***. Dec 2023;80:105093. doi:10.1016/j.msard.2023.105093

[18] Tzanetakos D, Tzartos JS, Vakrakou AG, et al. Cortical involvement and leptomeningeal inflammation in myelin oligodendrocyte glycoprotein antibody disease: A three-dimensional fluid-attenuated inversion recovery MRI study. ***Mult Scler***. Apr 2022;28(5):718-729. doi:10.1177/13524585211034362

[19] Hoftberger R, Guo Y, Flanagan EP, et al. The pathology of central nervous system inflammatory demyelinating disease accompanying myelin oligodendrocyte glycoprotein autoantibody. ***Acta Neuropathol***. May 2020;139(5):875-892. doi:10.1007/s00401-020-02132-y

[20] Cobo-Calvo A, Ayrignac X, Kerschen P, et al. Cranial nerve involvement in patients with MOG antibody-associated disease. ***Neurol Neuroimmunol Neuroinflamm***. Mar 2019;6(2):e543. doi:10.1212/NXI.0000000000000543

[21] Vazquez Do Campo R, Stephens A, Marin Collazo IV, Rubin DI. MOG antibodies in combined central and peripheral demyelination syndromes. ***Neurol Neuroimmunol Neuroinflamm***. Nov 2018;5(6):e503. doi:10.1212/NXI.0000000000000503

[22] Wynford-Thomas R, Jacob A, Tomassini V. Neurological update: MOG antibody disease. ***J Neurol***. May 2019;266(5):1280-1286. doi:10.1007/s00415-018-9122-2

[23] Rechtman A, Brill L, Zveik O, et al. Volumetric Brain Loss Correlates With a Relapsing MOGAD Disease Course. ***Front Neurol***. 2022;13:867190. doi:10.3389/fneur.2022.867190

[24] Cobo-Calvo A, d'Indy H, Ruiz A, et al. Frequency of myelin oligodendrocyte glycoprotein antibody in multiple sclerosis: A multicenter cross-sectional study. ***Neurol Neuroimmunol Neuroinflamm***. Mar 2020;7(2)doi:10.1212/NXI.0000000000000649

[25] Reindl M, Rostasy K. Serum MOG IgG titres should be performed routinely in the diagnosis and follow-up of MOGAD: Yes. ***Mult Scler***. Jul 2023;29(8):926-927. doi:10.1177/13524585231172954

TOWARDS PERSONALIZED AND PRECISION MEDICINE IN COGNITIVE DISORDERS: RULING OUT ALZHEIMER'S PATHOLOGY IN PATIENTS WITH CLINICAL SUSPICION OF ALZHEIMER'S DISEASE.

Ioanna Tsantzali [1], Vasilios C. Constantinides [2], Athanasia Athanasaki [1], Stella Fanouraki [1], Fotini Boufidou [2], Sotirios G. Paraskevas [1], Christos Kroupis [3], Anastasios Bonakis [1], Georgios Tsivgoulis [1],[4], Elisabeth Kapaki [2] and George P. Paraskevas [1],[2]

[1] *2nd Department of Neurology, "Attikon" General University Hospital, School of Medicine, National and Kapodistrian University of Athens, 12462 Athens, Greece*
[2] *Neurochemistry and biological Markers Unit, 1st Department of Neurology, "Eginition" Hospital, School of Medicine, National and Kapodistrian University of Athens, 11528 Athens, Greece*
[3] *Department of Clinical Biochemistry, Attikon University Hospital, National and Kapodistrian University of Athens, 12461 Athens, Greece*
[4] *Department of Neurology, University of Tennessee Health Science Center, Memphis, TN 38163, USA*

Abstract
Clinical diagnosis of Alzheimer's disease (AD) may not be easy in everyday practice, either due to atypical presentations of AD, or due to amnestic-like presentations of non-AD cognitive disorders. We present 4 patients with clinical suspicion of AD presence, 2 of them with amnestic mild cognitive impairment, one with amnestic dementia and one with primary progressive aphasia of the logopenic type. The first three patients had significant atrophy of medial temporal lobe. However, classical cerebrospinal fluid (CSF) biomarkers, revealed a non-AD profile in all four. Classical CSF biomarkers may serve as a significant tool, helpful not only for confirming the presence of AD, but also for excluding AD in cases with such a clinical suspicion. This may be significant when new, disease—modifying treatments are considered for the treatment of such patients.

Keywords: Alzheimer's disease; cognitive disorders; dementia; vascular cognitive disorder; cerebrospinal fluid.

ΟΔΕΥΟΝΤΑΣ ΠΡΟΣ ΤΗΝ ΠΡΟΣΩΠΟΠΟΙΗΜΕΝΗ ΙΑΤΡΙΚΗ ΚΑΙ ΤΗΝ ΙΑΤΡΙΚΗ ΑΚΡΙΒΕΙΑΣ ΣΤΙΣ ΓΝΩΣΙΑΚΕΣ ΔΙΑΤΑΡΑΧΕΣ: ΑΠΟΚΛΕΙΣΜΟΣ ΤΗΣ ΠΑΘΟΛΟΓΙΑΣ ΝΟΣΟΥ ALZHEIMER ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΛΙΝΙΚΗ ΥΠΟΨΙΑ ΤΗΣ ΝΟΣΟΥ.

Ιωάννα Τσαντζαλή[1], Βασίλειος Κωνσταντινίδης[2], Αθανασία Αθανασάκη[1], Στέλλα Φανουράκη[1], Φωτεινή Μπουφίδου[2], Σωτήριος Παρασκευάς[1], Χρήστος Κρούπης[3], Αναστάσιος Μπονάκης[1], Γεώργιος Τσιβγούλης[1],[4], Ελισσάβετ Καπάκη[2] και Γεώργιος Παρακευάς[1],[2]

[1] *Β' Νευρολογική Κλινική ΕΚΠΑ, ΠΓΝ «Αττικόν»*
[2] *Τμήμα Νευροχημείας και Βιολογικών Δεικτών, Α' Νευρολογική Κλινική ΕΚΠΑ, Αιγινήτειο Νοσοκομείο*
[3] *Τμήμα Κλινικής Βιοχημείας,ΕΚΠΑ, ΠΓΝ «Αττικόν»,*
[4] *Department of Neurology, University of Tennessee Health Science Center, Memphis, USA*

Περίληψη:
Η κλινική διάγνωση της νόσου Alzheimer μπορεί να αποτελεί πρόκληση στην καθ' ημέρα πράξη, είτε λόγω άτυπων εκδηλώσεων της ίδιας της νόσου, είτε λόγω εκδήλωσης άλλων, μη-Alzheimer γνωσιακών διαταραχών, με αμνησικό πρότυπο. Παρουσιάζουμε τέσσερις ασθενείς με κλινική υποψία νόσου Alzheimer, 2 εκ των οποίων με αμνησική ήπια γνωσιακή διαταραχή, ένας με αμνησικού τύπου άνοια και ένας με πρωτοπαθή προϊούσα αφασία λογοπενικού τύπου. Οι πρώτοι τρεις ασθενείς παρουσίαζαν σημαντική ατροφία του μέσου κροταφικού λοβού. Εντούτοις, οι κλασσικοί βιοδείκτες ΕΝΥ ανέδειξαν μη Alzheimer παθολογία και στους τέσσερις ασθενείς. Οι κλασσικοί βιοδείκτες ΕΝΥ μπορούν να λειτουργήσουν σαν ένα σημαντικό βοήθημα, όχι μόνο για την επικύρωση της παρουσίας παθολογίας νόσου Alzheimer αλλά ακόμη και για τον αποκλεισμό αυτής σε περιπτώσεις ασθενών με κλινική υποψία της νόσου, λαμβάνοντας ιδιαίτερα υπόψιν και την προοπτική χρήσης νέων, νοσοτροποποιητικών παραγόντων για τη θεραπεία αυτών των ασθενών.

Λέξεις ευρετηρίου: Νόσος Αλτσχάιμερ,νοητικές διαταραχές, άνοια, ανοσοαγγειακή νοητική διαταραχή,εγκεφαλονωτιαίο υγρό

1. Introduction

Alzheimer's disease (AD) is the most common cause of cognitive decline and it can be diagnosed either in the mild cognitive impairment (MCI) or in the dementia stage by the use of clinically based criteria [1,2]. However, atypical presentations of AD may occur [3] including, among others, frontal or posterior presentations and primary progressive aphasia (PPA) of the logopenic type [4]. In the presence of such atypical presentations, in early disease, in the community and in the presence of comorbidities, it is long known that clinical diagnostic accuracy may drop substantially [5] and, up to 39% of patients in which a non-AD diagnosis was given during life, will prove to have AD at autopsy [6]. The opposite is also true and, up to 30% of patients diagnosed with AD, will prove to have a non-AD pathology at neuropathological examination [7]. Thus, in vivo clinical diagnosis of AD is probabilistic and postmortem verification (or ruling out) remains the gold standard for final diagnosis. Primary age-related tauopathy (PART) [8] and limbic-predominant age-related TDP-43 encephalopathy (LATE) [9] are two pathologies which may present in the elderly as cognitive decline of the hippocampal amnestic type or "AD-type" dementia.

During the last decade, the 3 "established" or "classical" cerebrospinal fluid (CSF) biomarkers for AD have been incorporated in diagnostic criteria/guidelines [1,3] and classification systems [10]: (a) Amyloid-β peptide with 42 amino acids ($A\beta_{42}$) which is decreased in AD, is considered as a marker of amyloid plaque pathology [11], (b) tau protein phosphorylated to a threonine residue at position 181 ($\tau_{P\text{-}181}$) which is increased in AD, is considered as a marker of tangle formation [12] and (c) total tau protein (τ_T) which is increased in AD is a nonspecific marker of neuronal and/or axonal degeneration [13]. The $A\beta_{42}/A\beta_{40}$ ratio may be preferred to $A\beta_{42}$ alone since it seems to perform diagnostically better than the latter [14]. With a sensitivity and specificity at the level of ≥ 90% [3], they are useful in identifying the "AD neurochemical fingerprint" in atypical [15–18] or mixed [18–20] cases.

The aim of the present study is to describe a series of patients with a clinical presentation suggestive of AD, in which, however, CSF biomarkers ruled out the "AD neurochemical fingerprint", indicating a non-AD pathology.

2. Patients and Methods

2.1. Patients

Patients presented here were examined at the 2nd Department of Neurology ("Attikon" Hospital). They had cognitive impairment with presentation typical for, or highly suggestive of AD. Initially, history, neurological and complete physical examination were recorded routinely. Secondary causes including thyroid disease, B12 deficiency, neurosyphilis, brain tumor, subdural hematoma or normal pressure hydrocephalus were excluded. Initial clinical diagnosis was performed according to widely accepted criteria for MCI or dementia due to AD [1,2], for PPA [21], for Vascular cognitive impairment (VCI) [22] and for the behavioral variant of Frontotemporal Dementia (FTDbv) [23]. A written informed consent was obtained for all cases. The study had the approval of the Bioethics Committee (157/16-03-2021) and the Scientific Board (A13/07-04-2021) of "Attikon" Hospital and was conducted according to the ethical guidelines of the 1964 Declaration of Helsinki.

2.2. Neuropsychological testing

Following history and clinical examination a battery of neuropsychological tests was used, as routinely performed in our department. Global tests for assessment of cognition and activities of daily living included the Addenbrooke's Cognitive Examination-Revised version (ACE-R), the Mini Mental State Examination (MMSE), the Clinical Dementia Rating (CDR, both sum of boxes and overall score) and the Instrumental Activities of Daily Living (IADL) [24-27]. Brief tests for memory (free and cued recall), frontal function, visuospatial skills and depression included the 5-words memory test [28], the Frontal Assessment Battery (FAB) [29], the CLOX (1 and 2) [30] and the short version of the Geriatric Depression Scale (GDS) [31], respectively.

2.3. Neuroimaging

A routine 1.5 or 3T brain magnetic resonance imaging (MRI) scan was available for all patients, including 3D T1W sequences, suitable for assessing cortical and central atrophy. Medial Temporal lobe Atrophy (MTA) was assessed according to the Medial Temporal Atrophyvisual scale [32]. The recently introduced Entorhinal Cortex Atrophy Score (ERICA) was also determined at the level of the mammillary bodies [33,34].

2.4. Lumbar puncture and CSF biomarker measurements

According to widely accepted recommendations on standardized operative procedures for CSF biomarkers [35], lumbar puncture was performed using a standard, 21-22G, Quincke type needle, at the L4-L5 interspace, at 9-12 a.m. In brief, CSF was collected in 6 polypropylene tubes, as described elsewhere [17]. The 1st and 2nd tubes (1 ml each) were used for routine CSF cytology and biochemistry, respectively. The 3rd tube (2 ml) was used for oligoclonal bands and IgG index determinations. The following 2 tubes (5 ml each) were used for biomarker determinations. The last tube (~2 ml) was used for syphilis serology or other tests according to clinical indications. All

CSF samples had < 500 red blood cells/μL. The 2 tubes intended for CSF biomarker analysis, were immediately centrifuged (2000g×15 min), aliquoted in polypropylene tubes (1 ml each) and finally stored at –80°C. Aliquots were thawed only once, just before analysis, which was performed within 3 months of storage.

Classical CSF biomarkers ($A\beta_{42}$, $A\beta_{40}$, $\tau_{P\text{-}181}$ and τ_T) were measured in a Euroimmun Analyzer I (Euroimmun, Lübeck, Germany), in duplicate, with double sandwich enzyme-linked immunosorbent assay (ELISA) by commercially available kits [EUROIMMUN Beta-Amyloid (1- 42) ELISA, EUROIMMUN Beta-Amyloid (1- 40) ELISA, EUROIMMUN pTau(181) ELISA and EUROIMMUN Total-Tau ELISA respectively, Euroimmun, Lübeck, Germany], according to manufacturer's instructions and by the use of 4-parameter logistic curves as described elsewhere[16]. All procedures were performed under a stable temperature (21 ± 2 °C) and quality control samples (both in-house and provided by the manufacturer) were used in each run. The inter- and intra-assay coefficients of variation were both < 7% for all biomarkers. All assays were performed at the Unit of Neurochemistry and Biological Markers of the 1st Department of Neurology ("Eginition" Hospital) and, according to the cut-off values of our laboratory, biomarker concentrations were considered abnormal when $A\beta_{42}$<480 pg/ml, $A\beta_{42}/A\beta_{40}$< 0.094, $\tau_{P\text{-}181}$>60 pg/ml and τ_T>400 pg/ml, $\tau_{P\text{-}181}/A\beta_{42}$> 0.205 and $\tau_T/A\beta_{42}$> 0.710 [16,17].

Based on CSF biomarker concentrations and the presence or absence of atrophy on structural neuroimaging, the profile of each patient was determined according to the AT(N) classification system [10], as already described and diagrammatically illustrated elsewhere [17]. The CSF AD profile ("neurochemical fingerprint") was defined as decreased $A\beta_{42}$ or decreased $A\beta_{42}/A\beta_{40}$ and increased $\tau_{P\text{-}181}$ and thus, compatible with the $A^+T^+(N)^+$ or $A^+T^+(N)^-$ profiles [10]. On the contrary, the $A^-T^-(N)^+$ or $A^-T^+(N)^+$ profiles were considered compatible with non-AD pathology [10].

Genotyping of ***APOE*** was performed at the Department of Clinical Biochemistry of "Attikon" Hospital. Genomic DNA was extracted from 200 μl of blood using the "High Pure PCR Template Kit" (Roche, Mannheim, Germany). For the amplification of the ***APOE*** gene, 30 ng of genomic DNA was amplified using a "real-time qPCR kit" (TIB MolBiol, Berlin, Germany) in the "Light Cycler PCR" platform (Roche, Mannheim, Germany).

3. Results

All 4 reported patients had normal routine CSF cytology and biochemistry, normal IgG index and absence of oligoclonal bands, or any indication of neurosyphilis. Their demographic, clinical, neuropsychological and CSF neurochemical data are summarized in Table 1.

3.1. Patient 1

A 69 years-old male reported difficulty with recent memory during the last 3 years. He frequently repeated the same questions and needed to keep memos, but otherwise led an independent life, with no difficulty in every-day living. No family history of cognitive disorder was reported. The clinical picture was attributed to "depression" by a psychiatrist and mirtazapine 30 mg every night at bedtime was prescribed with no effect. Clinical and neurological examination was essentially normal. Neuropsychological examination revealed a hippocampal amnestic pattern, while a frontal component was also present. Neuroimaging (Figure 1a) revealed parietal cortical atrophy and involvement of the medial temporal lobe with an Medial Temporal Atrophygrade of at least 2 and an ERICA score of 2, indicating significant entorhinal cortex atrophy, which has been suggested to be compatible with AD [33,34]. A few, mild white matter lesions were observed, which were considered insignificant. The clinical picture was considered compatible with MCI due to AD [1]. However, CSF biomarkers revealed abnormal levels of only $\tau_{P\text{-}181}$ with no amyloid positivity. Thus, his AT(N) profile was $A^-T^+(N)^+$ (neurodegeneration was positive due to atrophy), indicating non-AD pathological change [10]. He was heterozygote for the ε2 allele of ***APOE***.

3.2. Patient 2

This is an 83 years-old male with a history of hypertension under losartan and hydrochlorothiazide. He reported difficulty with recent memory during the last 1.5 year. He keeps memos and frequently repeats the same questions, but otherwise he can perform relatively complex tasks such as handling money and banking and there was no difficulty with activities of everyday living. No family history of cognitive disorder was reported. Clinical examination revealed indifferent plantar responses but was otherwise normal. Neuropsychological examination revealed a hippocampal amnestic pattern, while a frontal component was also present. Neuroimaging (Figure 1b) revealed significant load of white mater lesions. Frontal and parietal cortical atrophy was also present together with involvement of the medial temporal lobe, with an Medial Temporal Atrophygrade of at least 2 and an ERICA score of 2, indicating significant entorhinal cortex atrophy, which has been suggested to be compatible with AD [33,34]. The clinical picture was considered compatible with MCI due to AD [1], with subcortical small vessel disease (SSVD). However, CSF analysis revealed normal levels of all 3 classical biomarkers. Thus, his AT(N) profile was $A^-T^-(N)^+$ (neurodegeneration was positive due to atrophy),

Table 1. Demographic, clinical, imaging and neurochemical data of the 4 patients.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Gender	male	male	male	female
Age (years)	69	83	53	63
Education (years)	6	6	16	15
Disease duration (years)	3	1.5	5	2
ACE-R [24]	73/100	65/100	71/100	76/100
MMSE [25]	26/30	25/30	22/30	26/30
CDR sum of boxes [26]	3	1.5	6	0.5
CDR overall [26]	0.5	0.5	1	0.5
IADL [27]	8/8	8/8	3/8	8/8
5-words delayed recall [28]	2+0/5	3+0/5	0+0/5	4+1/5
FAB [29]	11/18	12/18	16/18	11/18
CLOX1 [30]	9/15	10/15	10/15	9/15
CLOX2 [30]	15/15	13/15	14/15	13/15
GDS [31]	8/15	1/15	8/15	2/15
MTA grade [32]	2-3	3	4	0
ERICA score [33]	2	2	3	1
Vascular component (MRI)	Minimal	Significant	No	No
Initial clinical diagnosis	MCI due to AD	MCI due to AD plus SSVD	Dementia due to AD	PPA logopenic, probably due to AD
APOE	ε2 / ε3	ε2 / ε2	Not available	ε3 / ε3
$A\beta_{42}$ (pg/ml) (abnormal < 480)	830	1310	612	1102
$A\beta_{40}$ (pg/ml)	6657	7169	2892	7118
$A\beta_{42}/A\beta_{40}$ (abnormal < 0.094)	0.125	0.183	0.211	0.155
$\tau_{P\text{-}181}$ (pg/ml) (abnormal > 60)	62.9 ↑	54.7	19.6	75.7 ↑
τ_T (pg/ml) (abnormal > 400)	332	388	203	582 ↑
$\tau_{P\text{-}181}/A\beta_{42}$	0.076	0.042	0.032	0.069
$\tau_T/A\beta_{42}$	0.400	0.296	0.332	0.528
AT(N) profile [10]	$A^-T^+(N)^+$	$A^-T^-(N)^+$	$A^-T^-(N)^+$	$A^-T^+(N)^+$
Final diagnosis	Non-AD (tauopathy?)	VCI alone or mixed with non-AD pathology	Non-AD (FTLD?)	Non-AD (FTLD-tau?)

ACE-R: Addenbrooke's Cognitive Examination-Revised, MMSE: Mini Mental State Examination, CDR: Clinical Dementia Rating, IADL: Instrumental Activities of Daily Living, FAB: Frontal Assessment Battery, GDS: Geriatric Depression Scale, MRI: Magnetic Resonance Imaging, MCI: Mild Cognitive Impairment, SSVD subcortical small vessel disease, PPA: Primary Progressive Aphasia, FTLD: Frontotemporal Lobar Degeneration. ↑ Increased (abnormal) levels.

indicating non-AD pathological change [10]. He was homozygote for the ε2 allele of ***APOE***.

3.3. Patient 3

A 53 years-old male with no family history, developed difficulty with recent memory 5 years ago. Difficulty with complex tasks and orientation in place and time was gradually added, together with apathy. No inappropriate, perseverative or compulsive behavior, disinhibition, loss of empathy and sympathy or language disorder were reported. Some increase in appetite with weight gain (5 kg) was noted. At the time of examination, he was dependent to a significant degree and needed the care of his mother, at least partially. Neurological examination revealed brisk tendon reflexes symmetrically and

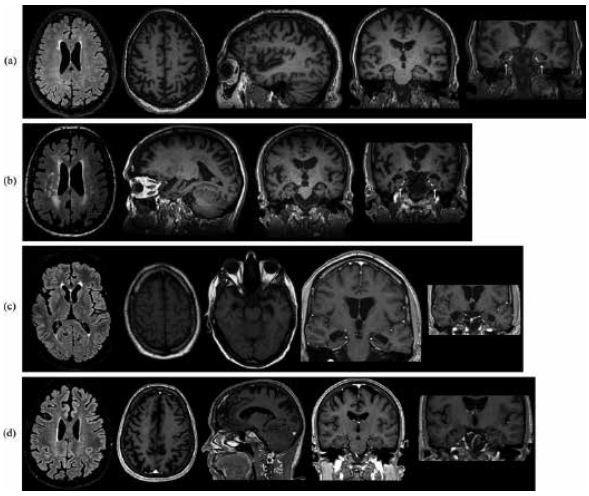


Figure 1. Magnetic resonance imaging of the 4 patients presented. (a) patient 1, (b) patient 2, (c) patient 3 and (d) patient 4. In (a) and (b): arrows indicate widening of the collateral sulcus and arrowheads indicate the "tentorial cleft sign", compatible with significant entorhinal cortex atrophy [33,34]

bilateral extensor plantar response, but no primitive reflexes. Neuropsychological examination showed a significant hippocampal amnestic disorder, while a frontal component was also present. Visuoconstructive abilities were preserved. Neuroimaging (Figure 1c) revealed significant atrophy of the hippocampal formation with an Medial Temporal Atrophygrade of 4 and an ERICA score of 3, indicating significant entorhinal cortex atrophy, which has been suggested to be compatible with AD [33,34]. Left anterior temporal atrophy was also observed. The clinical picture was considered compatible with dementia due to AD [2]. However, CSF analysis revealed normal levels of all 3 classical biomarkers. Thus, his AT(N) profile was $A^-T^-(N)^+$ (neurodegeneration was positive due to atrophy), indicating non-AD pathological change [10].

3.4. Patient 4

A 63 years-old right-handed female reported a language impairment during the last 2 years. She had a relatively decreased fluency due to word-finding difficulty. No significant impairment in other cognitive domains was reported by her or her relatives. She was completely independent and she could still work as a fashion designer. The only difficulty in everyday life was due to the language difficulty. Clinical examination was essentially normal. On neuropsychological testing frequent stops in spontaneous speech were noted in an effort to find the appropriate words. Phonological errors were not infrequent and repetition was definitely impaired. Motor and grammatical/structural aspects of speech, single word comprehension and object knowledge were preserved. Some degree of difficulty in frontal tests was observed and, additionally, there was an impression of possible apraxia in mimicking hand or finger movements, but none of these was reflected in visuospatial ability, everyday life and professional aspects. Graphesthesia and stereognosis were normal. Neuroimaging (Figure 1d) revealed parietal cortical atrophy with preservation of medial temporal lobe. Some degree of medial frontal atrophy was also observed. The clinical diagnosis was that of logopenic variant PPA [21], with the notable imaging finding of predominantly right (and not left) parietal atrophy. Although AD is the most common underlying pathology in logopenic PPA [4], CSF biomarkers revealed abnormal levels of $\tau_{P\text{-}181}$ and τ_T with no amyloid positivity. Thus, her AT(N) profile was $A^-T^+(N)^+$, indicating non-AD pathological change [10]. She was homozygote for the ε3 allele of ***APOE***.

4. Discussion

In the present study we present a series of 4 cognitively impaired patients with a clinical presentation typical for or suggestive of AD as the underlying pathology. However, CSF biomarkers showed normal amyloid levels in the form of both $A\beta_{42}$ alone and the $A\beta_{42}/A\beta_{40}$ ratio, which is considered to better reflect brain amyloid status [14]. Thus, according to the AT(N) classification system, AD or Alzheimer's continuum was excluded in all four and a diagnosis of non-AD pathological change was supported [10].

The 1st patient was considered to suffer of MCI due to AD, since the neuropsychological impairment was compatible mainly with the hippocampal amnestic type and there was medial temporal atrophy especially involving the entorhinal cortex in a significant degree (ERICA score 2). This clinical and imaging presentation would be considered rather typical for AD. However, CSF biomarkers, revealed the $A^-T^+(N)^+$ profile which, despite of various controversies and possible overlapping pathologies [36,37], it could be suggestive of a tauopathy. The patient was in the senile age (onset of symptoms > 65 years), but not at an age > 80 years. However, PART [8], which is a 3- and 4-repeat tauopathy [38] is a tempting diagnosis, since it has been observed not only in the oldest old [39], but also in "younger" old patients [40].

A debate exists as to whether PART is a completely different entity or, somehow, it belongs to the Alzheimer's spectrum [37]. Indeed, patients with the A^-T^+ profile may share some clinical, neuropsychological and imaging similarities with those with the typical AD profile (A^+T^+) [40]. However, some studies identify significant differences between PART and AD, especially slower rates of cognitive decline [39,41], lower ***APOE***ε4 frequency [39–42] and higher ***APOE***ε2 frequency [39,42] in PART, suggesting that at least a subgroup of PART patients does not belong to the Alzheimer's spectrum. Our patient had the ***APOE***ε2 and no ε4

allele, which could offer some resistance to Aβ formation and thus to AD, as previously suggested [42]. The (co)existence in our patient of argyrophilic grain disease [38,43] or ageing-related tau astrogliopathy [44], (both 4-repeat tauopathies) could be alternative diagnostic possibilities, as well as coexistence of PART with LATE [9].

But, is really the A^-T^+ profile (using $\tau_{P\text{-}181}$ for T) indicative of PART? It has been suggested that abnormal levels of $\tau_{P\text{-}181}$ may provide different information in cognitively impaired as compared to cognitively unimpaired subjects and in different clinical settings [45]. In a recent study, subjects with either the A^-T^+ or the A^-T^- profile had similar rates of cognitive decline and showed similar findings in the temporal lobes in Positron Emission Tomography for tau (tau-PET), suggesting that an elevated $\tau_{P\text{-}181}$ in the absence of Aβ abnormality may not necessarily reflect tangle formation, but may be related to altered CSF turnover/kinetics [46]. However, data on this field are few and conflicting.

The 2nd patient had significant subcortical small vessel disease (evident in neuroimaging). However, since (a) frontal dysfunction was not the prominent one, (b) he did not have significant apathy or depression, (c) he did not have any urinary symptoms such as frequency and/or urgency and (d) he did not suffer of any type of gait disorder, he did not fulfill the VASCOG criteria for predominant vascular etiology of cognitive impairment [22]. The hippocampal amnestic pattern in neuropsychological testing, combined with cortical and medial temporal/entorhinal cortex atrophy, lead to the impression of AD with concurrent SSVD. Biomarker levels in the CSF did not support this diagnosis and, the $A^-T^-(N)^+$ profile could be suggestive of VCI alone [1]. However, atrophy in the medial temporal lobe structures, raises the possibility of a concurrent neurodegenerative pathology. It seems that LATE may be the more plausible for this 83-year-old patient [9]. LATE is a distinct type of TDP-43 proteinopathy affecting the amygdala, the hippocampal formation including the entorhinal cortex and spreading to the temporal cortex, insula, orbitofrontal cortex and middle frontal gyrus [9]. It typically results in an amnestic syndrome which may gradually affect many cognitive domains. He did not show imaging characteristics of hippocampal sclerosis, but this is not required [9]. On the other hand, PART cannot be totally excluded, since not all cases of tauopathy are necessarily accompanied by increased CSF levels of $\tau_{P\text{-}181}$ [47]. Our patient had a $\tau_{P\text{-}181}/\tau_T$ ratio of 0.141; in our laboratory, values < 0.163 have been suggested as indicative of TDP-43 (and not tau) pathology in non-AD patients, but this is only speculative [15]. Both PART and LATE may coexist in the same patient [48]. Our patient was homozygote for the ***APOE***ε2 allele, but results on the ***APOE*** status in LATE are conflicting and the exact role of ε4 in cases of LATE without concomitant AD pathology remains to be elucidated [9]. Recent findings suggest that ***APOE***ε2 may have a protective role against multiple concurrent neurodegenerative pathologies [49], while it may exacerbate TDP-43 toxicity in the absence of concurrent AD pathology [50].

The 3rd patient developed an amnestic dementia at the presenium. Significant apathy was present, but this is observed in roughly 50% of patients with AD [51]. Mild hyperphagia with weight gain could be a red flag, but he did not fulfill even the criteria for possible FTDbv [23]. Thus, based on the amnestic neuropsychological profile and the significant atrophy of the hippocampal formation, he was initially considered as a presenile case of AD. Biomarker analysis revealed the $A^-T^-(N)^+$ profile. Frontotemporal lobar degeneration would be the most suitable diagnosis, given the asymmetric (left) anterior temporal lobe atrophy. Episodic memory disorder, despite being the hallmark of AD, it can be observed in FTDbv, sometimes causing diagnostic difficulties, especially in early cases [52]. Hippocampal atrophy can also be seen in some patients with FTD [53]. This patient's $\tau_{P\text{-}181}/\tau_T$ ratio was 0.097, which is very low for the cut-offs of our[15] and other laboratories [54], suggesting a possible TDP-43 pathology, but is insecure to theorize based solely on this ratio.

The 4th patient was different. She developed a rather typical logopenic-type language disorder, which was the only cause of difficulty in everyday life and, with a duration of 2 years fulfills the clinical criteria of logopenic PPA [21]. The mild apraxic signs were observed only during examination, they were not accompanied by any apraxic symptoms in everyday life and such signs have been reported in logopenic PPA patients, especially those due to AD [55]. At least 50%–56% and probably 76% of logopenic PPA patients have AD pathology, based in pathological data[4,56,57]. Studies based on biomarkers show a percentage of about 75%–79% [15,55,58]. She was ***APOE*** ε3 homozygote, but it has been observed that the percentage of ***APOE*** ε4 carriers in PPA due to AD is not increased as compared to controls and is lower as compared to the amnestic phenotypes of AD [59]. Thus, for our patient, AD seemed to be the most probable diagnosis. However, CSF biomarker analysis revealed the $A^-T^+(N)^+$ profile, which may be suggestive of tauopathy. Pathological data suggest that, following AD, neurodegenerative disorders with decreasing order of frequency are FTLDTDP-43, FTLD-tau and a combination of the two [56]. Indeed, non-AD logopenic patients have been reported to suffer of tau [60], TDP-43 [61], or even Lewy body [62] pathology.

In all four patients the use of CSF biomarkers (together with atrophy in neuroimaging) as suggested by the AT(N) classification system excluded AD or

Alzheimer's spectrum as the cause of their disorder. However, the exact cause was only partially suspected in the presence of the $A^-T^+(N)^+$ profile, possibly pointing to tauopathy, but not clarifying which one. In the case of the $A^-T^-(N)^+$ profile no diagnosis of inclusion can be made. Other biomarkers may be useful in this context. Imaging biomarkers include both amyloid- and tau-PET may be of help as they may not only differentiate between AD and non-AD cases in hippocampal amnestic patients, but may detect tauopathy restricted to medial temporal lobes, which corresponds to PART [63]. A combination of MRI and PET may prove helpful in the identification of LATE[64]. Assessment of CSF TDP-43, either alone or in combination with τ_T and $\tau_{P\text{-}181}$ [65], may also be useful in identifying TDP-43 pathology in FTLD patients[66] and increased TDP-43 levels in astrocyte-derived extracellular vesicles in plasma may prove useful tool in identifying patients with LATE [67]. Plasma progranulin concentration may help in identifying FTLD patients with possible mutations in the ***GRN*** gene [68]. Neurofilament light protein (NfL, a nonspecific marker of neuronal/axonal injury) and neurogranin (a marker of synaptic dysfunction) may offer additional information in some patients [69]. Concentration of CSF α-synouclein, although traditionally thought as marker of synucleinopathy [70] is an emerging rather than an established biomarker, since data are conflicting, the various forms of α-synouclein may show differences among various neurodegenerative disorders [71] and methodological issues remain to be addressed [72]. Furthermore, recent evidence suggests that a-synuclein may be a biomarker of AD and it is involved in the pathogenesis of this disorder [73,74].

5. Conclusions

Classical CSF biomarkers may serve as a significant tool, helpful not only for confirming the presence of AD, but also for excluding AD in cases with such a clinical suspicion. Sometimes they may provide a clue for the underlying non-AD pathology and sometimes not. However, even the exclusion of AD presence in otherwise typical AD-like patients may be significant if and when new, disease—modifying treatments are considered for the treatment of such patients.

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Institutional Review Board Statement: The study had the approval of the Bioethics Committee and the Scientific Board of "Attikon" Hospital (approval numbers 157/16-03-2021 and A13/07-04-2021, respectively). It was performed according to the 1964 Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study and/or next of kin caregivers (depending on the severity of cognitive impairment).

Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available due to privacy restrictions.

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References

[1] Albert, M.S.; DeKosky, S.T.; Dickson, D.; Dubois, B.; Feldman, H.H.; Fox, N.C. et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. ***Alzheimers Dement.*****2011,***7,*** 270-279.

[2] McKhann, G.M.; Knopman, D.S.; Chertkow, H.; Hyman, B.T.; Jack, C.R. Jr.; Kawas, C.H.; et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. ***Alzheimers Dement.*****2011;***7,*** 263-269.

[3] Dubois, B.; Feldman, H.H.; Jacova, C.; Hampel, H.; Molinuevo, J.L.; Blennow, K.; et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. ***Lancet Neurol.*****2014,***13***, 614-629.

[4] Grossman, M. Primary progressive aphasia: clinicopathological correlations. ***Nat. Rev. Neurol.*****2010,***6,*** 88-97.

[5] Mendez, M.; Mastri, A.R.; Sung, J.H.; Frey, W.H. Clinically diagnosed Alzheimer's disease: neuropathologic findings in 650 cases. ***Alzheimer Dis. Assoc. Disord.*****1992;***6,*** 35-43.

[6] Galasko, D.; Hansen, L.A.; Katzman, R.; Wiederholt, W.; Masliah, E.; Terry, R.; et al. Clinical-neuropathological correlations in Alzheimer's disease and related dementias. ***Arch. Neurol.*****1994,***51,*** 888-895.

[7] Nelson, P.T.; Head, E.; Schmitt, F.A.; Davis, P.R.; Neltner, J.H.; Jicha, G.A.; et al. Alzheimer's disease is not "brain aging": neuropathological,

genetic, and epidemiological human studies. ***Acta Neuropathol.*****2011,***121,* 571-587.

[8] Crary, J.F.; Trojanowski, J.Q.; Schneider, J.A.; Abisambra, J.F.; Abner, E.L.; Alafuzoff, I.; et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. ***Acta Neuropathol.*** **2014,** *128,* 755-766.

[9] Nelson, P.T.; Dickson, D.W.; Trojanowski, J.Q.; Jack, C.R.; Boyle, P.A.; Arfanakis, K.;et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report. ***Brain*****2019,** *142,* 1503-1527.

[10] Jack, C.R. Jr.; Bennett, D.A.; Blennow, K.; Carrillo, M.C.; Dunn, B.; Haeberlein, S.B.; et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. ***Alzheimers Dement.*****2018,***14,* 535-562.

[11] Sjögren, M.; Minthon, L.; Davidsson, P.; Granérus, A.K.; Clarberg, A.; Vanderstichele, H.; et al. CSF levels of tau, beta-amyloid(1-42) and GAP-43 in frontotemporal dementia, other types of dementia and normal a***ging. J. Neural Transm.*** (Vienna) **2000,***107,* 563-579.

[12] Vanderstichele, H.; De Vreese, K.; Blennow, K.; Andreasen, N.; Sindic, C.; Ivanoiu, A.; et al. Analytical performance and clinical utility of the INNOTEST PHOSPHO-TAU181P assay for discrimination between Alzheimer's disease and dementia with Lewy bodies. ***Clin. Chem. Lab. Med.*****2006,***44,* 1472-1480.

[13] Blennow, K.; Wallin, A.; Agren, H.;, Spenger, C.; Siegfried, J.; Vanmechelen, E. Tau protein in cerebrospinal fluid: a biochemical marker for axonal degeneration in Alzheimer disease? ***Mol. Chem. Neuropathol.*****1995,***26,* 231-245.

[14] Niemantsverdriet, E.; Ottoy, J.; Somers, C.; De Roeck, E.; Struyfs, H.; Soetewey, F.; et al. The Cerebrospinal Fluid Aβ1-42/Aβ1-40 Ratio Improves Concordance with Amyloid-PET for Diagnosing Alzheimer's Disease in a Clinical Setting. ***J. Alzheimers Dis.*****2017,***60,* 561-576.

[15] Paraskevas, G.P.; Kaselimis, D.; Kourtidou, E.; Constantinides, V.; Bougea, A.; Potagas, C.; et al. Cerebrospinal Fluid Biomarkers as a Diagnostic Tool of the Underlying Pathology of Primary Progressive Aphasia. ***J. Alzheimer's Dis.*****2017,***55,* 1453–1461.

[16] Constantinides, V.C.; Paraskevas, G.P.; Boufidou, F.; Bourbouli, M.; Stefanis, L.; Kapaki, E. Cerebrospinal fluid biomarker profiling in corticobasal degeneration: Application of the AT(N) and other classification systems. ***Parkinsonism Relat. Disord.*****2021,** *82,* 44–49.

[17] Tsantzali, I.; Boufidou, F.; Sideri, E.; Mavromatos, A.; Papaioannou, M.G.; Foska, A.; et al. From Cerebrospinal Fluid Neurochemistry to Clinical Diagnosis of Alzheimer's Disease in the Era of Anti-Amyloid Treatments. Report of Four Patients. ***Biomedicines*****2021**, *9,* 1376.

[18] Paraskevas, G.P.; Constantinides, V.C.; Boufidou, F.; Tsantzali, I.; Pyrgelis, E.S.; Liakakis, G.; Kapaki, E. Recognizing Atypical Presentations of Alzheimer's Disease: The Importance of CSF Biomarkers in Clinical Practice. ***Diagnostics*****2022**, *12,* 3011.

[19] Theodorou, A.; Tsantzali, I.; Kapaki, E.; Constantinides, V.C.; Voumvourakis, K.; Tsivgoulis, G.; Paraskevas, G.P. Cerebrospinal fluid biomarkers and apolipoprotein E genotype in cerebral amyloid angiopathy. A narrative review. ***Cereb. Circ. Cogn. Behav.*****2021,***2,* 100010.

[20] Foska, A.; Tsantzali, I.; Sideri, E.; Stefanou, M.I.; Bakola, E.; Kitsos, D.K.; et al. Classical Cerebrospinal Fluid Biomarkers in Dementia with Lewy Bodies. ***Medicina*****2022**, *58,* 612.

[21] Gorno-Tempini, M.L.; Hillis, A.E.; Weintraub, S.; Kertesz, A.; Mendez, M.; Cappa, S.F.; et al. Classification of primary progressive aphasia and its variants. ***Neurology*****2011,***76,* 1006-1014.

[22] Sachdev, P.; Kalaria, R.; O'Brien, J.; Skoog, I.; Alladi, S.; Black, S.E.; et al. Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. ***Alzheimer Dis. Assoc. Disord.*****2014**, *28*, 206-218.

[23] Rascovsky, K.; Hodges, J.R.; Knopman, D.; Mendez, M.F.; Kramer, J.H.; Neuhaus, J.; et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. ***Brain*** **2011,***134*, 2456–2477.

[24] Konstantinopoulou, E.; Kosmidis, M.H.; Ioannidis, P.; Kiosseoglou, G.; Karacostas, D.; Taskos, N. Adaptation of Addenbrooke's Cognitive Examination-Revised for the Greek population. ***Eur. J. Neurol.*****2011,***18,* 442–447

[25] Fountoulakis, K.N.; Tsolaki, M.; Chantzi, H.; Kazis, A. Mini Mental State Examination (MMSE): A validation study in Greece. ***Am. J. Alzheimers Dis. Other Demen.*****2000,***15,* 342–345.

[26] Morris, J.C. The Clinical Dementia Rating (CDR): current version and scoring rules. ***Neurology*****1993,** *43,* 2412–2414.

[27] Theotoka, I.; Kapaki, E.; Vagenas, V.; Ilias, I.; Paraskevas, G.P.; Liappas, I. Preliminary report of a validation study of Instrumental Activities of Daily Living in a Greek sample. ***Percept. Mot. Skills.*****2007,***104,* 958–960.

[28] Dubois, B.; Touchon, J.; Portet, F.; Ousset, P.J.; Vellas, B.; Michel, B. "The 5 words": a simple and sensitive test for the diagnosis of Alzheimer's disease. ***Presse. Med.*****2002,***31,* 1696–1699.

[29] Dubois, B.; Slachevsky, A.; Litvan, I.; Pillon, B. The FAB: a Frontal Assessment Battery at bedside. ***Neurology*****2000,***55,* 1621–1626.

[30] Royall, D.R.; Cordes, J.A.; Polk, M. CLOX: an

executive clock drawing task. ***J. Neurol. Neurosurg. Psychiatry*1998,*64,*** 588–594.
[31] Sheikh, J.I.; Yesavage, J.A. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. ***Clinical Gerontologist*1986,*5***, 165–173.
[32] Scheltens, P.; Leys, D.; Barkhof, F.; Huglo, D.; Weinstein, H.C.; Vermersch, P.; et al. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. ***J. Neurol. Neurosurg. Psychiatry*1992,*55,*** 967–972.
[33] Enkirch, S.J.; Traschütz, A.; Müller, A.; Widmann, C.N.; Gielen, G.H.; Heneka, M.T.; et al. The ERICA Score: An MR Imaging-based Visual Scoring System for the Assessment of Entorhinal Cortex Atrophy in Alzheimer Disease. ***Radiology*2018**, ***288,*** 226–233.
[34] Traschütz, A.; Enkirch, S.J.; Polomac, N.; Widmann, C.N.; Schild, H.H.; Heneka, M.T.; Hattingen, E. The Entorhinal Cortex Atrophy Score Is Diagnostic and Prognostic in Mild Cognitive Impairment. ***J. Alzheimers Dis.*2020**, ***75***, 99–108.
[35] Del Campo, M.; Mollenhauer, B.; Bertolotto, A.; Engelborghs, S.; Hampel, H.; Simonsen, A.H.; et al. Recommendations to standardize preanalytical confounding factors in Alzheimer's and Parkinson's disease cerebrospinal fluid biomarkers: an update. ***Biomark. Med.*2012,*6,*** 419–430.
[36] Yoon, B.; Guo, T.; Provost, K.; Korman, D.; Ward, T.J.; Landau, S.M.; Jagust, W.J.; Alzheimer's Disease Neuroimaging Initiative. Abnormal tau in amyloid PET negative individuals. ***Neurobiol. Aging*2022,*109***, 125–134.
[37] Weigand, A.J.; Bangen, K.J.; Thomas, K.R.; Delano-Wood, L.; Gilbert, P.E.; Brickman, A.M.; Bondi, M.W.; Alzheimer's Disease Neuroimaging Initiative. Is tau in the absence of amyloid on the Alzheimer's continuum?: A study of discordant PET positivity. ***Brain Commun.*2020**, ***2***, fcz046.
[38] Rawat, P.; Sehar, U.; Bisht, J.; Selman, A.; Culberson, J.; Reddy, P.H. Phosphorylated Tau in Alzheimer's Disease and Other Tauopathies. ***Int. J. Mol. Sci.*2022,*23***, 12841.
[39] Savola, S.; Kaivola, K.; Raunio, A.; Kero, M.; Mäkelä, M.; Pärn, K.; et al. Primary age-related tauopathy in a Finnish population-based study of the oldest old (Vantaa 85+). ***Neuropathol. Appl. Neurobiol.*2022**, ***48,*** e12788.
[40] Weigand, A.J.; Edwards, L.E.; Thomas, K.R.; Bangen, K.J.; Bondi, M.W.; Alzheimer's Disease Neuroimaging Initiative. Comprehensive characterization of elevated tau PET signal in the absence of amyloid-beta. ***Brain Commun***. **2022**, ***4,*** fcac272.
[41] Bell, W.R.; An, Y.; Kageyama, Y.; English, C.; Rudow, G.L.; Pletnikova, O.; Thambisetty, M.; et al. Neuropathologic, genetic, and longitudinal cognitive profiles in primary age-related tauopathy (PART) and Alzheimer's disease. ***Alzheimers Dement.*** **2019**, ***15***, 8–16.
[42] McMillan, C.T.; Lee, E.B.; Jefferson-George, K.; Naj, A.; Van Deerlin, V.M.; Trojanowski, J.Q.; Wolk, D.A. Alzheimer's genetic risk is reduced in primary age-related tauopathy: a potential model of resistance? ***Ann. Clin. Transl. Neurol.*2018**, ***5***, 927–934.
[43] Jellinger, K.A. Recent update on the heterogeneity of the Alzheimer's disease spectrum. ***J. Neural Transm.*2022**, ***129***, 1–24.
[44] McCann, H.; Durand, B.; Shepherd, C.E. Aging-Related Tau Astrogliopathy in Aging and Neurodegeneration. ***Brain Sci.*2021**, ***11***, 927.
[45] Mattsson-Carlgren, N.; Leuzy, A.; Janelidze, S.; Palmqvist, S.; Stomrud, E.; Strandberg, O.; et al. The implications of different approaches to define AT(N) in Alzheimer disease. ***Neurology*2020,*94***, e2233–e2244.
[46] Erickson, P.; Simrén, J.; Brum, W.S.; Ennis, G.E.; Kollmorgen, G.; Suridjan, I.; et al. Prevalence and Clinical Implications of a β-Amyloid-Negative, Tau-Positive Cerebrospinal Fluid Biomarker Profile in Alzheimer Disease. ***JAMA Neurol.*2023**, e232338. doi: 10.1001/jamaneurol.2023.2338. Online ahead of print.
[47] Constantinides, V.C.; Paraskevas, G.P.; Emmanouilidou, E.; Petropoulou, O.; Bougea, A.; Vekrellis, K.; et al. CSF biomarkers beta-amyloid, tau proteins and a-synuclein in the differential diagnosis of Parkinson-plus syndromes. ***J. Neurol. Sci***. **2017**, ***382***, 91–95.
[48] Nelson, P.T.; Brayne, C.; Flanagan, M.E.; Abner, E.L.; Agrawal, S.; Attems, J.; et al. Frequency of LATE neuropathologic change across the spectrum of Alzheimer's disease neuropathology: combined data from 13 community-based or population-based autopsy cohorts. ***Acta Neuropathol.*2022**, ***144***, 27–44.
[49] Walker, J.M.; Richardson, T.E. Cognitive resistance to and resilience against multiple comorbid neurodegenerative pathologies and the impact of APOE status. ***J. Neuropathol. Exp. Neurol.*2022**, nlac115. doi: 10.1093/jnen/nlac115. Online ahead of print.
[50] Meneses, A.D.; Koga, S.; Li, Z.; O'Leary, J.; Li, F.; Chen, K.; et al. APOE2 Exacerbates TDP-43 Related Toxicity in the Absence of Alzheimer Pathology. ***Ann. Neurol.*2022**, doi: 10.1002/ana.26580. Online ahead of print.
[51] Zhao, Q.F.; Tan, L.; Wang, H.F.; Jiang, T.; Tan, M.S.; Tan, L.; et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. ***J. Affect.***

Disord. **2016**, *190*, 264–271.
[52] Korhonen, T.; Katisko, K.; Cajanus, A.; Hartikainen, P.; Koivisto, A.M.; Haapasalo, A.; et al. Comparison of Prodromal Symptoms of Patients with Behavioral Variant Frontotemporal Dementia and Alzheimer Disease. ***Dement. Geriatr. Cogn. Disord.*****2020**, *49*, 98–106.
[53] Poos, J.M.; Grandpierre, L.D.M.; van der Ende, E.L.; Panman, J.L.; Papma, J.M.; Seelaar, H.; et al. Longitudinal Brain Atrophy Rates in Presymptomatic Carriers of Genetic Frontotemporal Dementia. ***Neurology*****2022**, *99*, e2661–2671.
[54] Borroni, B.; Benussi, A.; Archetti, S.; Galimberti, D.; Parnetti, L.; Nacmias, B.; et al. Csf p-tau181/tau ratio as biomarker for TDP pathology in frontotemporal dementia. ***Amyotroph. Lateral Scler. Frontotemporal. Degener***. **2015,***16*, 86–91.
[55] Teichmann, M.; Kas, A.; Boutet, C.; Ferrieux, S.; Nogues, M.; Samri, D.; et al. Deciphering logopenic primary progressive aphasia: a clinical, imaging and biomarker investigation. ***Brain*****2013,***136,* 3474–3488.
[56] Mesulam, M.M.; Weintraub, S.; Rogalski, E.J.; Wieneke, C.; Geula, C.; Bigio, E.H. Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. ***Brain*****2014,***137,* 1176–1192.
[57] Bergeron, D.; Gorno-Tempini, M.L.; Rabinovici, G.D.; Santos-Santos, M.A.; Seeley,W.; Miller, B.L.; et al. Prevalence of amyloid-β pathology in distinct variants of primary progressive aphasia. ***Ann. Neurol.*****2018**, *84*, 729–740.
[58] Santangelo, R.; Coppi, E.; Ferrari, L.; Bernasconi, M.P.; Pinto, P.; Passerini, G.; et al. (2015) Cerebrospinal fluid biomarkers can play a pivotal role in the diagnostic work up of primary progressive aphasia***. J. Alzheimers Dis.*** **2015**, *43*, 1429–1440.
[59] Weintraub, S.; Teylan, M.; Rader, B.; Chan, K.C.G.; Bollenbeck, M.; Kukull, W.A.; Coventry, C.; et al.***APOE*** is a correlate of phenotypic heterogeneity in Alzheimer disease in a national cohort. ***Neurology*****2020**, *94*, e607–612.
[60] Momota, Y.; Konishi, M.; Takahata, K.; Kishimoto, T.; Tezuka, T.; Bun, S.; et al. Case report: Non-Alzheimer's disease tauopathy with logopenic variant primary progressive aphasia diagnosed using amyloid and tau PET. ***Front. Neurol.*****2022**, *13*, 1049113.
[61] Kim, G.; Ahmadian, S.S.; Peterson, M.; Parton, Z.; Memon, R.; Weintraub, S.; et al. Asymmetric pathology in primary progressive aphasia with progranulin mutations and TDP inclusions. ***Neurology*****2016,***86,* 627–636.
[62] Boes, S.; Botha, H.; Machulda, M.; Lowe, V.; Graff-Radford, J.; Whitwell, J.L.; et al. Dementia with Lewy bodies presenting as Logopenic variant primary progressive Aphasia. ***Neurocase*****2020**, *26*, 259–263.
[63] Lagarde, J.; Olivieri, P.; Tonietto, M.; Gervais, P.; Comtat, C.; Caillé, F.; et al. Distinct amyloid and tau PET signatures are associated with diverging clinical and imaging trajectories in patients with amnestic syndrome of the hippocampal type. ***Transl. Psychiatry*****2021,** *11,* 498.
[64] Duong, M.T.; Wolk, D.A. Limbic-Predominant Age-Related TDP-43 Encephalopathy: LATE-Breaking Updates in Clinicopathologic Features and Biomarkers. ***Curr. Neurol. Neurosci. Rep.*****2022**, *22*, 689–698.
[65] Bourbouli, M.; Rentzos, M.; Bougea, A.; Zouvelou, V.; Constantinides, V.C.; Zaganas, I.; et al. Cerebrospinal Fluid TAR DNA-Binding Protein 43 Combined with Tau Proteins as a Candidate Biomarker for Amyotrophic Lateral Sclerosis and Frontotemporal Dementia Spectrum Disorders. ***Dement. Geriatr. Cogn. Disord***. **2017**, *44*, 144–152.
[66] Kapaki, E.; Boufidou, F.; Bourbouli, M.; Pyrgelis, E.S.; Constantinides, V.C.; Anastassopoulou, C.; Paraskevas, G.P. Cerebrospinal Fluid Biomarker Profile in TDP-43-Related Genetic Frontotemporal Dementia. ***J. Pers. Med.*****2022**, *12*, 1747.
[67] Winston, C.N.; Sukreet, S.; Lynch, H.; Lee, V.M.; Wilcock, D.M.; Nelson, P.T.; Rissman, R.A. Evaluation of blood-based, extracellular vesicles as biomarkers for aging-related TDP-43 pathology. ***Alzheimers Dement***. **2022**, *14,* e12365.
[68] Bourbouli, M.; Paraskevas, G.P.; Rentzos, M.; Mathioudakis, L.; Zouvelou, V.; Bougea, A.; et al. Genotyping and Plasma/Cerebrospinal Fluid Profiling of a Cohort of Frontotemporal Dementia-Amyotrophic Lateral Sclerosis Patients. ***Brain Sci***. **2021**, *11,* 1239.
[69] Rådestig, M.A.; Skoog, J.; Zetterberg, H.; Skillbäck, T.; Zettergren, A.; Sterner, T.R.; et al. Subtle Differences in Cognition in 70-Year-Olds with Elevated Cerebrospinal Fluid Neurofilament Light and Neurogranin: A H70 Cross-Sectional Study. ***J. Alzheimers Dis.*****2023**, *91*, 291–303.
[70] Chalatsa, I.; Melachroinou, K.; Emmanouilidou, E.; Vekrellis, K. Assesment of cerebrospinal fluid α-synuclein as a potential biomarker in Parkinson's disease and synucleinopathies. ***Neuroimmunol. Neuroinflammation*** **2020**, *7*, 132–140.
[71] Constantinides, V.C.; Majbour, N.K.; Paraskevas, G.P.; Abdi, I.; Safieh-Garabedian, B.; Stefanis, L.; et al. Cerebrospinal Fluid α-Synuclein Species in Cognitive and Movements Disorders. ***Brain Sci.*****2021**, *11,* 119.
[72] Anagnostou, D.; Sfakianaki, G.; Melachroinou, K.; Soutos, M.; Constantinides, V.; Vaikath, N.; et al. Assessment of Aggregated and Exosome-

Associated α-Synuclein in Brain Tissue and Cerebrospinal Fluid Using Specific Immunoassays. ***Diagnostics*2023**, ***13***, 2192.

[73] Li, J.Q.; Bi, Y.L.; Shen, X.N.; Wang, H.F.; Xu, W.; Tan, C.C.; et al. Cerebrospinal fluid α-synuclein predicts neurodegeneration and clinical progression in non-demented elders. ***Transl. Neurodegener.*2020,*9,*** 41.

[74] Shim, K.H.; Kang, M.J.; Youn, Y.C.; An, S.S.A.; Kim, S. Alpha-synuclein: a pathological factor with Aβ and tau and biomarker in Alzheimer's disease. ***Alzheimers Res. Ther.*** **2022**, ***14***, 201.

ΒΡΑΧΕΙΑ ΣΥΣΤΗΜΑΤΙΚΗ ΑΝΑΣΚΟΠΗΣΗ ΤΗΣ ΑΙΜΟΦΑΓΟΚΥΤΤΑΡΙΚΗΣ ΛΕΜΦΟΪΣΤΙΟΚΥΤΤΑΡΩΣΗΣ ΑΠΟ ΛΑΜΟΤΡΙΓΙΝΗ

Θεοχάρης Κυζιρίδης

Γ΄Ψυχιατρική Κλινική ΑΠΘ, ΠΓΝΘ «ΑΧΕΠΑ»

Περίληψη

Σκοπός: Από το 2018, η Αμερικανική Επιτροπή Τροφίμων και Φαρμάκων έχει προειδοποιήσει για τον κίνδυνο αιμοφαγοκυτταρικής λεμφοϊστιοκυττάρωσης (ΑΛ) από λαμοτριγίνη. Σκοπός της εργασίας είναι να απαντήσει, μέσα από τη μελέτη τέτοιων περιπτώσεων, στο κατά πόσο η λήψη λαμοτριγίνης σχετίζεται με την εμφάνιση ΑΛ.

Υλικό-Μέθοδος: Ακολουθήθηκαν οι οδηγίες PRISMA για την εκπόνηση συστηματικής ανασκόπησης. Οι εργασίες ταυτοποιήθηκαν με αναζήτηση στις βάσεις δεδομένων PubMed και Science Direct με συμπληρωματική αναζήτηση στο Google Scholar. Χρησιμοποιήθηκαν οι όροι («Lamotrigine» OR «Lamotrigine-induced») AND («Hemophagocytic Lymphohistiocytosis» OR «Hemophagocytic Syndrome») και αναζητήθηκαν αναφορές περιπτώσεων και πρακτικά συνεδρίων. Ελέγχθηκαν τίτλοι και περιλήψεις όλων των εργασιών και βρέθηκαν τα πλήρη κείμενα όσων τελικά συμπεριλήφθηκαν στο άρθρο.

Αποτελέσματα: Ανευρέθηκαν 81 εργασίες από τις οποίες 49 ήταν διπλότυπες. Από τις υπόλοιπες 32 εργασίες οι μισές αφαιρέθηκαν μετά από ανάγνωση τίτλου και περίληψης (οι 10) ή του πλήρους κειμένου (οι 6). Από τις 16 μελέτες στις οποίες περιγράφονται ισάριθμες περιπτώσεις ασθενών, οι 4 αφορούσαν άτομα παιδικής-εφηβικής ηλικίας και οι υπόλοιπες 12 ενήλικους ασθενείς. Από την πρώτη ομάδα η δόση της λαμοτριγίνης αναφέρθηκε σε 2 από τις 4 περιπτώσεις και θεωρήθηκε υψηλή για παιδιά. Το χρονικό διάστημα που μεσολάβησε από την έναρξη του φαρμάκου μέχρι την εκδήλωση των συμπτωμάτων ΑΛ ήταν 18,25 ημέρες. Από τους ενήλικους ασθενείς, η δόση της λαμοτριγίνης που οδήγησε στην εμφάνιση ΑΛ αναφέρθηκε σε 3 από τις 12 περιπτώσεις και ήταν χαμηλή (25-50 mg). Το χρονικό διάστημα που μεσολάβησε μέχρι την εμφάνιση ΑΛ αναφέρθηκε σε 10 από τις 12 περιπτώσεις και ήταν κατά μέσο όρο 11,3 ημέρες.

Συμπεράσματα: Η ΑΛ από λαμοτριγίνη είναι σπάνια αλλά απαιτεί έγκαιρη διάγνωση και κατάλληλη αντιμετώπιση αλλιώς μπορεί να οδηγήσει ακόμη και στον θάνατο. Η δόση του φαρμάκου δεν φαίνεται να διαδραματίζει κάποιο ρόλο και η εμφάνιση της διαταραχής γίνεται συνήθως μέσα στις πρώτες 3 εβδομάδες από την έναρξή του.

Λέξεις ευρετηρίου: Αιμοφαγοκυτταρική λεμφοϊστιοκυττάρωση, Αιμοφαγοκυτταρικό σύνδρομο, Λαμοτριγίνη, Φαρμακοεπαγόμενες ανεπιθύμητες ενέργειες

BRIEF SYSTEMATIC REVIEW OF LAMOTRIGINE-INDUCED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Theocharis Chr. Kyziridis

3rd University Department of Psychiatry, «AHEPA» University Hospital of Thessaloniki

Abstract

Aim: Since 2018 FDA has issued a warning concerning the risk of hemophagocytic lymphohistiocytosis (HL) induced by lamotrigine. The aim of this article is to answer, through the study of such cases, whether lamotrigine administration is related to HL.

Material-Method: We followed the PRISMA guidelines and we conducted a systematic search of PubMed and Science Direct, with complementary search of Google Scholar, including case reports and congress abstracts, using the terms («Lamotrigine» OR «Lamotrigine-induced») AND («Hemophagocytic Lymphohistiocytosis» OR «Hemophagocytic Syndrome»). All titles and abstracts were screened, and the full texts of relevant studies were obtained.

Results: We found 81 papers of which 49 were duplicate. Among the 32 papers, half were removed based

on title and abstract (10) or full text reading (6). From the 16 papers which describe 16 case reports, 4 concerned children and adolescents and the remaining 12 concerned adult patients. Among children and adolescents, the dose of lamotrigine was mentioned in 2 cases and was considered to be high. The time interval between lamotrigine initiation and LH manifestation was 18.25 days. Among the adult patients, the lamotrigine dose that induced HL was low (25-50 mg) and mentioned in only 3 cases. The time interval between lamotrigine initiation and LH manifestation was on average 11.3 days.

Conclusions: Lamotrigine-induced HL is rare but timely diagnosis and proper treatment is essential, otherwise it may even lead to death. The dose of the drug does not seem to play a role and the manifestation of HL usually takes place within the first 3 weeks.

Key words: Drug-induced side-effects, Hemophagocytic lymphohistiocytosis, Hemophagocytic syndrome, Lamotrigine

ΕΙΣΑΓΩΓΗ

Η αιμοφαγοκυτταρική λεμφοϊστιοκυττάρωση (ΑΛ) ή αιμοφαγοκυτταρικό σύνδρομο είναι σπάνια, οξεία, ταχέως εξελισσόμενη συστηματική φλεγμονώδης διαταραχή της οποίας διακρίνονται δύο μορφές: μια πρωτοπαθής, με γενετικό υπόβαθρο, και μια δευτεροπαθής, με εκλυτικούς παράγοντες κακοήθεις νεοπλασίες, λοιμώξεις, αυτοάνοσες διεργασίες ή, λιγότερο συχνά, φάρμακα. Χαρακτηρίζεται από παγκυτταροπενία, αυξημένη παραγωγή κυτταροκινών και αυξημένα επίπεδα φερριτίνης (Πίνακας 1).[1,2] Παθοφυσιολογικά πρόκειται για μη ελεγχόμενη ενεργοποίηση του ανοσοποιητικού συστήματος. Οι εκλυτικοί παράγοντες στη δευτεροπαθή μορφή της διαταραχής πιστεύεται ότι ενεργοποιούν τα μακροφάγα τα οποία φαγοκυτταρώνουν κύτταρα του αίματος και απελευθερώνουν μεγάλες ποσότητες προφλεγμονωδών κυτταροκινών με αποτέλεσμα καταιγίδα κυτταροκινών που προκαλεί πολλές βλάβες και μπορεί να οδηγήσει ακόμη και στον θάνατο.[3]

Πρόκειται για δύσκολη, στη διαχείρισή της, διαταραχή αφενός λόγω της αλληλεπικάλυψης που παρουσιάζει με πολλές άλλες κλινικές καταστάσεις και αφετέρου λόγω της αναγκαιότητας για έγκαιρη διάγνωση. Η έκβαση της νόσου στους ενήλικους ποικίλλει όμως η πρώιμη διάγνωση και η κατάλληλη αντιμετώπιση διαδραματίζουν σημαντικό ρόλο στον καθορισμό της.[4] Παρά τη θεραπευτική αντιμετώπιση, εκτιμάται πως, στους ενήλικους, τα ποσοστά θνητότητας αγγίζουν στην πρώιμη φάση περίπου το 20% και μπορούν συνολικά να φθάσουν το 40-50%.[1]

Πρόσφατα, στη βιβλιογραφία έχουν παρουσιαστεί περιπτώσεις φαρμακοεπαγόμενης ΑΛ από φάρμακα όπως η λαμοτριγίνη, ενώ, από το 2018, η Αμερικανική Επιτροπή Τροφίμων και Φαρμάκων (FDA) έχει προειδοποιήσει για ΑΛ από λαμοτριγίνη ζητώντας να προστεθεί προειδοποίηση στις συνταγογραφικές πληροφορίες του φαρμάκου και καλώντας τους επαγγελματίες υγείας να επαγρυπνούν με σκοπό την έγκαιρη διάγνωση και πρώιμη αντιμετώπιση του συνδρόμου ώστε να βελτιωθεί η έκβασή του και να ελαττωθεί η θνητότητα.[5]

Η λαμοτριγίνη είναι φάρμακο που χρησιμοποιείται τόσο στη νευρολογία όσο και στην ψυχιατρική. Είναι παράγωγο φαινυλτριαζίνης που αρχικά περιγράφηκε ως αντιεπιληπτικό φάρμακο. Είναι εγκεκριμένη ως θεραπεία σε διαταραχές όπως η εστιακή επιληψία, οι πρωτοπαθείς γενικευμένοι τονικο-κλονικοί σπασμοί, οι γενικευμένοι τονικο-κλονικοί σπασμοί του συνδρόμου Lennox-Gastaut, και ως θεραπεία συντήρησης στη διπολική διαταραχή Ι. Ο μηχανισμός δράσης της δεν είναι πλήρως κατανοητός αλλά πιθανώς οι κύριες δράσεις της σχετίζονται με προσυναπτικό ανταγωνισμό των τύπου 2 τασεοεξαρτωμένων διαύλων νατρίου.[6]

ΥΛΙΚΟ ΚΑΙ ΜΕΘΟΔΟΣ

Σκοπός της εργασίας είναι η διερεύνηση των περιπτώσεων φαρμακοεπαγόμενης ΑΛ από λαμοτριγίνη. Ακολουθήθηκαν οι οδηγίες PRISMA για την εκπόνηση της συστηματικής ανασκόπησης (Γράφημα 1).[7] Οι εργασίες ταυτοποιήθηκαν με αναζήτηση στις βάσεις δεδομένων PubMed και Science Direct με συμπληρωματική αναζήτηση στο Google Scholar. Η αναζήτηση πραγματοποιήθηκε τον Μάρτιο 2022 με τη χρήση των όρων («Lamotrigine» OR «Lamotrigine-induced») AND («Hemophagocytic Lymphohistiocytosis» OR «Hemophagocytic Syndrome»). Τέθηκε περιορισμός όσον αφορά το είδος των μελετών (αναφορές περιπτώσεων και πρακτικά συνεδρίων) αλλά όχι ως προς την ημερομηνία ή τη γλώσσα δημοσίευσης. Συμπεριλήφθηκαν περιπτώσεις για τις οποίες υπήρχε αιτιολογική σχέση μεταξύ λαμοτριγίνης και εκδήλωσης ΑΛ. Περιπτώσεις συνδρόμου DRESS ή φαρμακοεπαγόμενης αντίδρασης υπερευαισθησίας δεν συμπεριλήφθηκαν στη μελέτη.

Τα δεδομένα που συλλέχθηκαν περιελάμβαναν φύλο και ηλικία, ατομικό ψυχιατρικό και λοιπό αναμνηστικό, φαρμακευτική αγωγή, εκτός από τη λαμοτριγίνη, δόση της λαμοτριγίνης και χρονικό διάστημα μέχρι την εμφάνιση ΑΛ, κλινικά και εργαστηριακά ευρήματα από την εκδήλωση του συνδρόμου.

ΑΠΟΤΕΛΕΣΜΑΤΑ

Ανευρέθηκαν 81 εργασίες από τις οποίες 49 ήταν διπλότυπες. Από τις υπόλοιπες 32 εργασίες οι μισές

αφαιρέθηκαν μετά από ανάγνωση τίτλου και περίληψης (οι 10) ή του πλήρους κειμένου (οι 6) λόγω μη συνάφειας με το περιεχόμενο αυτής της εργασίας. Οι υπόλοιπες 16 συμπεριλήφθηκαν στην εργασία και το πλήρες κείμενο ανευρέθηκε από όλες (Πίνακας 2).[8-23]

Από τις 16 μελέτες στις οποίες περιγράφονται ισάριθμες περιπτώσεις ασθενών, οι 4 αφορούσαν άτομα παιδικής-εφηβικής ηλικίας[8-11] και οι υπόλοιπες 12 ενήλικους ασθενείς.[12-23] Τα άτομα της πρώτης ομάδας περιελάμβαναν 3 άρρενες και 1 θήλυ με μέση ηλικία 9 ετών (4-16 ετών). Τα 2 άτομα έπασχαν από επιληψία και τα άλλα 2 από ψυχιατρικές διαταραχές. Η δόση της λαμοτριγίνης αναφερόταν μόνο σε 2 από τις 4 περιπτώσεις και θεωρήθηκε υψηλή για παιδιά. Το χρονικό διάστημα που μεσολάβησε από την έναρξη του φαρμάκου μέχρι την εκδήλωση των συμπτωμάτων ΑΛ ήταν 18,25 ημέρες (14-24 ημέρες).

Οι Yang et al.[8] περιέγραψαν ότι χορηγήθηκε λαμοτριγίνη λόγω μη καλού ελέγχου σπασμών με τα υπόλοιπα αντιεπιληπτικά. Η δόση του φαρμάκου ελαττώθηκε αρχικά στα 50 mg ενώ, αργότερα κατά τη νοσηλεία, διακόπηκαν τελείως τόσο η λαμοτριγίνη όσο και το βαλπροϊκό. Οι Gumus et al.[9] ανέφεραν επίσης ότι προστέθηκε λαμοτριγίνη, λόγω μη καλού ελέγχου επιληπτικών σπασμών με τα υπόλοιπα αντιεπιληπτικά, η οποία ελαττώθηκε σταδιακά μέχρι τα 50 mg.Στην περίπτωση του 16χρονου έφηβου των Kita et al.,[10] είχε τεθεί αρχικά η διάγνωση φαρμακοεπαγόμενης αντίδρασης υπερευαισθησίας ενώ σε αυτή των Bechtel & Joyce[11] τέθηκε το διαγνωστικό ερώτημα της συνύπαρξης νόσου Kawasaki. Σε αυτή την τελευταία περίπτωση, η πορεία της 8χρονης ασθενούς παρουσίασε επιπλοκή με αρτηριακή υπέρταση και αναπνευστική καταστολή για την οποία χρειάστηκε μηχανικός αερισμός.

Από τους 12 ενήλικους ασθενείς, 7 ήταν άνδρες και 5 γυναίκες και η μέση ηλικία τους ήταν περίπου 35 έτη (26-47 έτη). Από αυτούς, 4 έπασχαν από επιληψία και 8 από ψυχιατρικές διαταραχές. Σε έναν ασθενή υπήρχε συννόσηση επιληψίας-ψυχιατρικών διαταραχών. Η δόση της λαμοτριγίνης που οδήγησε στην εμφάνιση ΑΛ αναφέρθηκε μόνο σε 3 από τις 12 περιπτώσεις και ήταν χαμηλή (25-50 mg). Το χρονικό διάστημα που μεσολάβησε μέχρι την εμφάνιση ΑΛ αναφέρθηκε σε 10 από τις 12 περιπτώσεις και ήταν κατά μέσο όρο 11,3 ημέρες (6-17 ημέρες). Σε 1 περίπτωση δεν αναφέρθηκε καθόλου και σε άλλη 1 αναφερόταν ότι ήταν λίγες ημέρες.

Οι Grenouillet et al.[12] περιέγραψαν περίπτωση που αρχικά έμοιαζε με αντίδραση υπερευαισθησίας ενώ ταυτόχρονα διαγνώστηκε και συστηματικός ερυθηματώδης λύκος (ΣΕΛ). Η λαμοτριγίνη διακόπηκε τη 17η ημέρα νοσηλείας. Ταυτόχρονη συνύπαρξη ΣΕΛ λύκου διαγνώστηκε και στην περίπτωση των Felzer et al.[20] κατά την οποία οι συγγραφείς έκαναν λόγο για σύνδρομο ενεργοποίησης μακροφάγων, ένα δευτεροπαθές σύνδρομο ΑΛ, επειδή απουσίαζε από τα εργαστηριακά ευρήματα η κλασική παγκυτταροπενία. Τα συμπτώματα του ασθενούς επέμεναν παρά τη διακοπή της λαμοτριγίνης και η πορεία του παρουσίασε επιπλοκές με οπισθοπεριτοναϊκή αιμορραγία, εμβολή, οξεία παγκρεατίτιδα και ντελίριο ενώ χρειάστηκε για κάποιες ημέρες και αιμοκάθαρση.

Παρατεταμένη νοσηλεία είχαν οι ασθενείς των Ignaszewski et al.[13] και Organti et al.[14] Στον πρώτο, ασθενή με χρόνια ψύχωση, η λαμοτριγίνη διακόπηκε κατά τη νοσηλεία ενώ η δεύτερη, ασθενής με κατάθλιψη, τη διέκοψε αυτοβούλως προ της εισαγωγής λόγω κεφαλαλγίας. Επιπλέον, χρειάστηκε νοσηλεία σε μονάδα εντατικής θεραπείας (ΜΕΘ) λόγω πιθανής μηνιγγίτιδας και υποογκαιμικού shock.

Σε ΜΕΘ νοσηλεύτηκε και η ασθενής των Aggarwal et al.[15] λόγω σοβαρής υπότασης. Στον ασθενή των Hancock & Galvez[16] έγινε αντικατάσταση της λαμοτριγίνης με λακοσαμίδη ενώ σε αυτήν των Tora et al.[17] η λαμοτριγίνη διακόπηκε. Η τελευταία διασωληνώθηκε καθώς παρουσίασε διάχυτη ενδαγγειακή πήξη.

Η ασθενής των Zhou et al.,[18] στην οποία η λαμοτριγίνη διακόπηκε κατά την εισαγωγή, εισήχθη για σήψη και οξεία υποξαιμική αναπνευστική ανεπάρκεια. Κατά την πορεία της νόσου, παρουσίασε μυοκαρδιοπάθεια Takotsubo και οξεία νεφρική ανεπάρκεια για την οποία χρειάστηκε αιμοκάθαρση. Ο ασθενής των Boustani et al.[19] ξεκίνησε διαδικασία για μεταμόσχευση λόγω σοβαρής ηπατικής βλάβης. Στον ασθενή των Suleman et al.[22] η λαμοτριγίνη διακόπηκε κατά την 1η ημέρα νοσηλείας, στον ασθενή των Koning et al.[21] διακόπηκε κατά τη νοσηλεία και των Velu et al.[23] κατά την εισαγωγή.

ΣΥΖΗΤΗΣΗ

Όπως προκύπτει από τα παραπάνω, πρακτικά όλοι οι ασθενείς είχαν πολυήμερες νοσηλείες, με πολλαπλές εξετάσεις και, σε αρκετές περιπτώσεις, σοβαρές επιπλοκές. Η ΑΛ είναι σοβαρή νόσος και είναι απαραίτητη η συνεχής επαγρύπνηση ώστε να ανιχνευτούν έγκαιρα και να αντιμετωπιστούν αποτελεσματικά περιπτώσεις του συνδρόμου.

Η λαμοτριγίνη σχετίζεται με ανεπιθύμητες ενέργειες ανοσολογικής φύσης, όπως είναι το σύνδρομο Stevens Johnson, το σύνδρομο DRESS, αιματολογικές δυσκρασίες και άσηπτη μηνιγγίτιδα.[24] Ο ακριβής μηχανισμός είναι μάλλον άγνωστος αλλά το φάρμακο φαίνεται ότι μπορεί να εκλύει ανοσολογικές αποκρίσεις μέσω ενεργοποίησης των Τ κυττάρων.[25] Έτσι, σε περιπτώσεις όπως αυτές που περιγράφηκαν παραπάνω, η λήψη λαμοτριγίνης θα πρέπει να λαμβάνεται σοβαρά υπόψη και το, αν και σπάνιο, σύνδρομο ΑΛ θα πρέπει να περιλαμβάνεται στη διαφορική διάγνωση ώστε να αντιμετωπιστεί όσο το δυνατόν πιο έγκαιρα. Μάλιστα, από τις 16 αναφορές περίπτωσης που ανευρέθηκαν, οι 11 δημοσιεύτηκαν από το 2018 και έπειτα, κάτι που μπορεί να δείχνει πως η προειδοποίηση του FDA για

τη σύνδεση λαμοτριγίνης και ΑΛ μπορεί να βοήθησε στην αύξηση της επαγρύπνησης των γιατρών.

Η δόση του φαρμάκου δεν φαίνεται να διαδραματίζει κάποιο ρόλο αν και οι πληροφορίες που παρασχέθηκαν σχετικά με αυτό ήταν ελλιπείς. Το χρονικό διάστημα εκδήλωσης της ΑΛ μετά την έναρξη λαμοτριγίνης είναι το αρχικό διάστημα και, πιο συγκεκριμένα, οι πρώτες 3 εβδομάδες.

Βιβλιογραφία

[1] Soy M, Atagündüz P, Atagündüz I, Türköz Sucak G. Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. *Rheumatol Int* 2021, 41: 7–18

[2] Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004. Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007, 48: 124-131

[3] George MR. Hemophagocytic lymphohistiocytosis: review of etiologies and management. *J Blood Med* 2014, 5: 69–86

[4] Ponnatt TS, Lilley CM, Mirza KM. Hemophagocytic lymphohistiocytosis. *Arch Pathol Lab Med* 2022, 146: 507–519

[5] Food and Drug Administration. FDA Drug Safety Communication: FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal). 04/25/2018. Accessed at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-serious-immune-system-reaction-seizure-and-mental-health, on March 11, 2022

[6] Rissardo JP, Fornari Caprara AL. Lamotrigine-associated movement disorder: A literature review. *Neurol India* 2021, 69: 1524-1538

[7] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021, 372: n71

[8] Yang Y-C, Jou S-T, Chang Y-H, Liang J-S, Lee W-T. Hemophagocytic syndrome associated with antiepileptic drug. *Pediatr Neurol* 2004, 30: 358-360

[9] 9. Gümü–H, Kumanda–S, Per H, Karakükçü M. Hemophagocytic syndrome associated with high-dose lamotrigine. *Pediatr Int* 2007, 49: 672-673

[10] 10. Kita K, Takeshita T, Matsuishi E, Furue M. A case of drug-induced hypersensitivity syndrome with hemophagocytic syndrome associated with lamotrigine. *Nishi Nihon Hifuka* 2014, 76: 324-329

[11] Bechtel AS, Joyce M. A case of hemophagocytic lymphohistiocytosis and Kawasaki disease: Concurrent or overlapping diagnoses? *J Pediatr Hematol Oncol* 2018, 40: e32-e33

[12] Grenouillet M, Camou F, Guisset O, Etienne G, Carmoi T, Dilhuydy MS, et al. Syndrome d'hypersensibilite et lupus induit par la lamotrigine. *Rev Med Interne* 2003, 24 (Suppl 4): 486s

[13] Ignaszewski M, Ignaszewski MJ, Kohlitz P. Lamotrigine-associated hemophagocytic lymphohistiocytosis. *Am J Ther* 2017, 24: e493

[14] Organti NK, Patolia S, Naydenov S. Rare case of hemophagocytic lymphohistiocytosis due to lamotrigine. *Crit Care Med* 2019, 47: 223

[15] Aggarwal M, Aggarwal D, Azharuddin S, Buirkle E. Inciting a storm in depression. *Chest* 2019, 156 (Suppl): A2135

[16] Hancock CL, Gálvez A. Lamotrigine-associated hemophagocytic lymphohistiocytosis. *Blood* 2019, 133: 1165

[17] Tora I, Rhea L, Holbrook M, Ershler W, Gami Y. Lamictal® and hemophagocytic lymphohistiocytosis (HLH). *Blood* 2019, 134 (Supplement 1): 4880

[18] Zhou JY, Martinez JA, Shen JP. Lamotrigine-induced hemophagocytic lymphohistiocytosis with Takotsubo cardiomyopathy: a case report. *J Med Case Rep* 2019, 13: 345

[19] Boustani CH, Stone BS, Patti A, Rangnekar AS. Drug induced liver injury and concurrent hemophagocytic lymphohistiocytosis after lamotrigine exposure. *Am J Gastroenterol* 2020, 115: S1318

[20] Felzer J, Kashani K, Odeyemi Y. Lamotrigine-induced lupus and macrophage activation syndrome: A diagnostic dilemma. *Chest* 2021, 160 (Suppl): A1

[21] Koning MT, Janmaat CJ, Peltenburg HG, Tiren-Verbeet NL. Lamotrigine-associated hemophagocytic lymphohistiocytosis. *J Clin Psychopharmacol* 2021, 41: 498-499

[22] Suleman N, Ozdemirli M, Weisman D. Lamotrigine-associated hemophagocytic lymphohistiocytosis. *BMJ Case Rep* 2021, 14: e238183

[23] Velu D, Kantamneni L, Batool SS, Hachem A. Lamotrigine-associated haemophagocytic lymphohistiocytosis (HLH) confounded with underlying rheumatoid arthritis. *BMJ Case Rep* 2022, 15: e245835

[24] GlaxoSmithKline. Lamictal (lamotrigine) prescribing information. Research Triangle Park, NC: GlaxoSmithKline; 2015

[25] Naisbitt DJ, Farrell J, Wong G, Depta JpH, Dodd CC, Hopkins JE, et al. Characterization of drug-specific T cells in lamotrigine hypersensitivity. *J Allergy Clin Immunol* 2003, 111: 1393-1403

Πίνακας 1. Διάγνωση αιμοφαγοκυτταρικής λεμφοϊστιοκυττάρωσης2

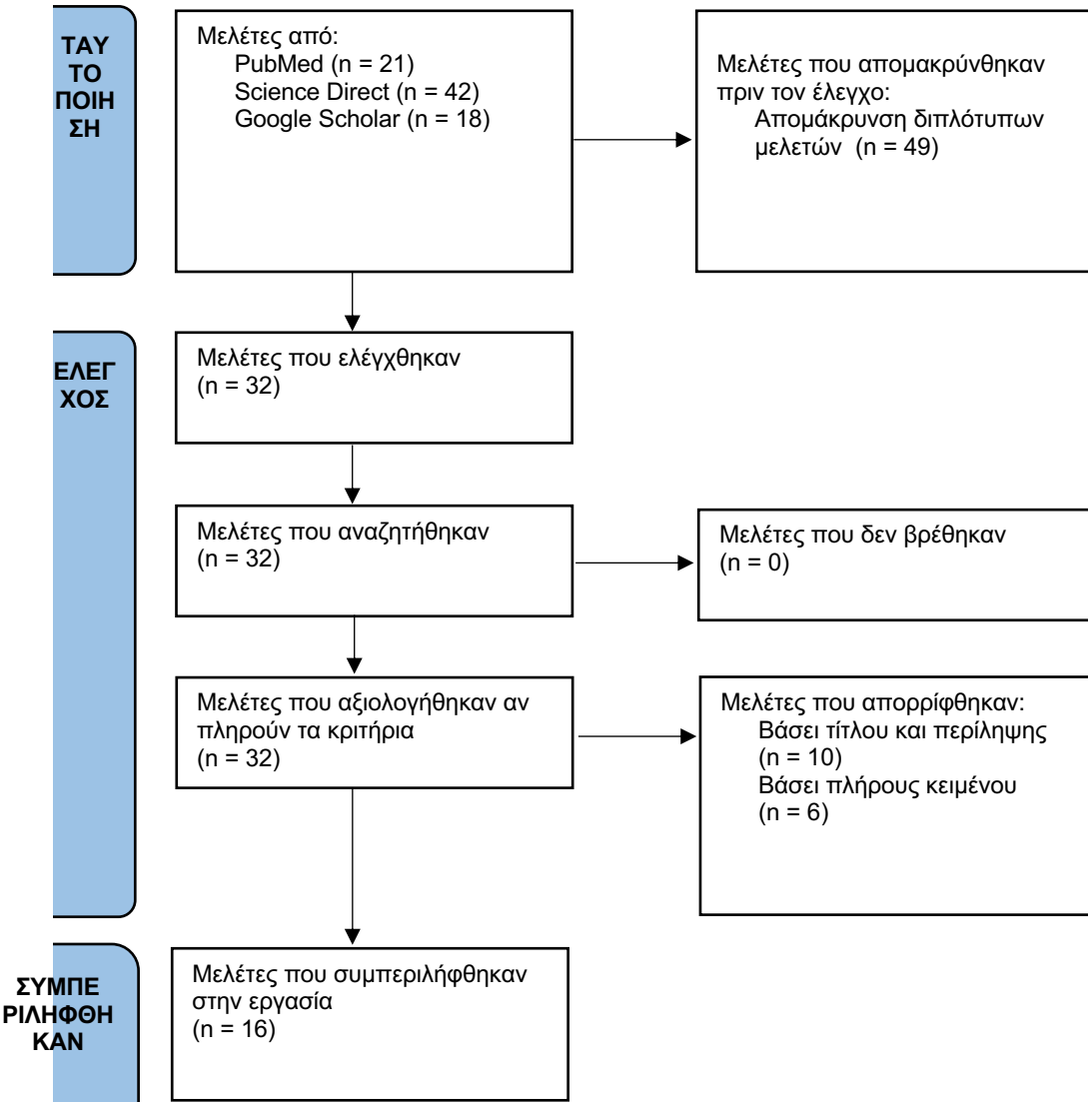
5 από τις 8 ακόλουθες εκδηλώσεις
Πυρετός
Κυτταροπενία σε δύο σειρές
Σπληνομεγαλία
Υπερτριγλυκεριδαιμία
Ελαττωμένο ινωδογόνο
Αυξημένη φερριτίνη
Χαμηλή ή απούσα δραστηριότητα κυττάρων φυσικών φονέων
Αυξημένη διαλυτή CD25
Επιπλέον ευρήματα
Τρανσαμινασαιμία
Διαταραχή πηκτικού μηχανισμού
Οίδημα
Εξάνθημα
Νευρολογικά συμπτώματα

Πίνακας 2. Αναφορές περιπτώσεων αιμοφαγοκυτταρικής λεμφοϊστιοκυττάρωσης από λαμοτριγίνη

Εργασία	Δημογραφικά	Ατομικό αναμνηστικό	Φαρμακευτική αγωγή (πλην λαμοτριγίνης)	Δόση λαμοτριγίνης και χρονικό διάστημα μέχρι την εμφάνιση συμπτωμάτων	Κύρια κλινικά και εργαστηριακά ευρήματα
Παιδιά-έφηβοι					
Yang et al. 2004[8]	Αγόρι 8 ετών	Επιληψία Πορεγκεφαλία (ΔΕ)	Τοπιραμάτη Βαλπροϊκό οξύ	100 mg	Πυρετός, κνησμώδες εξάνθημα, λήθαργος, ίκτερος, κοιλιακό άλγος, αιμορραγία στοματικής κοιλότητας
				2 εβδομάδες	Παγκυτταροπενία, τρανσαμινασαιμία, πλευριτική και ασκιτική συλλογή
Gumus et al. 2007[9]	Αγόρι 4 ετών	Επιληψία Εγκεφαλική παράλυση	Πριμιδόνη Βαλπροϊκό οξύ	250 mg	Πυρετός, εξάνθημα, ημικωματώδης κατάσταση, γενικευμένοι τονικο-κλονικοί σπασμοί, ίκτερος, ηπατοσπληνομεγαλία
				3 εβδομάδες	Παγκυτταροπενία, διαταραχή νεφρικής και ηπατικής λειτουργίας
Kita et al. 2014[10]	Έφηβος 16 ετών	Διπολική διαταραχή	Βαλπροϊκό νάτριο	Δεν αναφέρεται δόση	Ερύθημα προσώπου, πυρετός, αυχενική λεμφαδενοπάθεια
				2 εβδομάδες	Ηωσινοφιλία, ηπατική δυσλειτουργία

Bechtel & Joyce 2018[11]	Κορίτσι 8 ετών	Διαταραχή Ελλειμματικής Προσοχής-Υπερκινητικότητα Μη άλλως καθοριζόμενη συναισθηματική διαταραχή	Δεν αναφέρεται	Δεν αναφέρεται	Πυρετός, λεμφαδενοπάθεια, νεφρική δυσλειτουργία, γενικευμένοι τονικο-κλονικοί σπασμοί και εγκεφαλοπάθεια
				24 ημέρες	Αυξημένο PT, ινωδογόνο, μηδενική δραστηριότητα NK κυττάρων, πιθανό στεφανιαίο ανεύρυσμα
Ενήλικοι					
Grenouillet et al. 2003[12]	Άνδρας 29 ετών	Επιληψία	Δεν αναφέρεται	Δεν αναφέρεται	Πυρετός, μηνιγγικό σύνδρομο, εξάνθημα, στοματικά έλκη, φλεγμονώδης πολυαρθρίτιδα
				10 ημέρες	Χολόσταση – τρανσαμινασαιμία
Ignaszewski et al. 2017[13]	Άνδρας 26 ετών	Άγχος, παρανοϊκότητα	Ρισπεριδόνη Βενζοτροπίνη	Δεν αναφέρεται	Κακουχία, πυρετός, μώλωπες
				2 εβδομάδες	Παγκυτταροπενία, τρανσαμινασαιμία
Organti et al. 2018[14]	Γυναίκα 39 ετών	Κατάθλιψη Γαστροοισοφαγική παλινδρόμηση	Δεν αναφέρεται	Δεν αναφέρεται	Κεφαλαλγίες, γενικευμένη αδυναμία, πυρετός, οσφυαλγία
				Δεν αναφέρεται	Παγκυτταροπενία, αυξημένη χολερυθρίνη, LFTs
Aggarwal et al. 2019[15]	Γυναίκα 39 ετών	Κατάθλιψη	Δεν αναφέρεται	Δεν αναφέρεται	Πυρετός, φρίκια, υπόταση, ναυτία, έμετος, φωτοφοβία, κεφαλαλγία, αυχεναλγία
				1 εβδομάδα	Θρομβοπενία, αυξημένα ηπατικά ένζυμα, ελαττωμένα επίπεδα NK κυττάρων
Hancock & Galvez 2019[16]	Άνδρας 47 ετών	Ανθεκτική επιληψία	Δεν αναφέρεται	Δεν αναφέρεται	Πυρετός, εξάνθημα, σπληνομεγαλία
				Λίγες ημέρες	Τρανσαμινασαιμία, λευκοπενία
Tora et al. 2019[17]	Γυναίκα 27 ετών	Διπολική κατάθλιψη Άγχος	Δεν αναφέρεται	25 mg	Εξάνθημα, λήθαργος, κεφαλαλγία, δύσπνοια, ταχυκαρδία, πυρετός, βήχας
				6 ημέρες	Αυξημένες τρανσαμινάσες και χολερυθρίνη

Zhou et al. 2019[18]	Γυναίκα 45 ετών	Γενικευμένο άγχος Υποτροπιάζουσα κατάθλιψη	Αμλοδιπίνη Χολεκαλσιφερόλη Κλοναζεπάμη Ντουλοξετίνη Πραζοσίνη	Δεν αναφέρεται	Γριππώδες σύνδρομο με πυρετό και αυχενική δυσκαμψία, ταχυκαρδία, εξάνθημα
				Περίπου 10-17 ημέρες	Αναιμία, θρομβοπενία, τρανσαμινασαιμία, ηπατοσπληνομεγαλία, πλευριτικές συλλογές
Boustani et al. 2020[19]	Άνδρας 31 ετών	Επιληψία	Δεν αναφέρεται	Δεν αναφέρεται	Πυρετός, κόπωση, εξάνθημα, εγκεφαλοπάθεια
				14 ημέρες	Έκπτωση νεφρικής λειτουργίας, τρανσαμινασαιμία, ελαττωμένη δραστηριότητα NK κυττάρων, ηπατομεγαλία, θρομβοπενία
Felzer et al. 2021[20]	Άνδρας 34 ετών	Σύνδρομο Raynaud Διπολική κατάθλιψη	Δεν αναφέρεται	Δεν αναφέρεται	Δύσπνοια, ναυτία, πυρετός, ταχυκαρδία, υποξία, εξάνθημα, αιμορραγικές βλάβες στόματος
				10 ημέρες	Τρανσαμινασαιμία, νεφρική βλάβη-πρωτεϊνουρία
Koning et al. 2021[21]	Άνδρας 43 ετών	Διαταραχή αποπροσωποίησης-αποπραγματοποίησης	Βενλαφαξίνη	50 mg	Κεφαλαλγία, μυαλγίες, ναυτία, έμετος, πυρετός, δύσπνοια
				16 ημέρες	Τρανσαμινασαιμία, θρομβοπενία, πρωτεϊνουρία, ηπατοσπληνομεγαλία
Suleman et al. 2021[22]	Άνδρας 31 ετών	Διαταραχή Ελλειμματικής Προσοχής-Υπερκινητικότητα Επιληψία Δ/χη χρήσης αλκοόλ	Αμφεταμίνη Δεξτροαμφεταμίνη Λεβεταρακετάμη	50 mg	Πυρετός, φρίκια, ναυτία, έμετος, κεφαλαλγία, εξάνθημα
				11 ημέρες	Αναιμία, θρομβοπενία, τρανσαμινασαιμία, ελαττωμένη δραστηριότητα NK κυττάρων
Velu et al. 2022[23]	Γυναίκα, λίγο πριν τα 30	Ρευματοειδής αρθρίτιδα Μείζων κατάθλιψη	Δεν αναφέρεται	Δεν αναφέρεται	Πυρετός, μυαλγίες, λεμφαδενοπάθεια, εξάνθημα
				12 ημέρες	Λευκοπενία, λεμφοπενία, θρομβοπενία, αυξημένα ηπατικά ένζυμα, σπληνομεγαλία



Γράφημα 1. Διάγραμμα ροής