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Review

Diagnosis and treatment of late-onset myoclonic epilepsy in Down syndrome (LOMEDS): A systematic review with individual patients' data analysis

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ABSTRACT

Introduction: The late onset myoclonic epilepsy in Down Syndrome (LOMEDS) is a peculiar epilepsy type characterized by cortical myoclonus and generalized tonic-clonic seizures (GTCS), in people suffering from cognitive decline in Down syndrome (DS). In this review, we analyzed available data on the diagnostic and therapeutic management of individuals with LOMEDS.

Methods: We performed a systematic search of the literature to identify the diagnostic and therapeutic management of patients with LOMEDS. The following databases were used: PubMed, Google Scholar, EMBASE, CrossRef. The protocol was registered on PROSPERO (registration code: CRD42023390748).

Results: Data from 46 patients were included. DS was diagnosed according to the patient's clinical and genetic characteristics. Diagnosis of Alzheimer's dementia (AD) preceded the onset of epilepsy in all cases. Both myoclonic seizures (MS) and generalized tonic-clonic seizures (GTCS) were reported, the latter preceding the onset of MS in 28 cases. EEG was performed in 45 patients, showing diffuse theta/delta slowing with superimposed generalized spike-and-wave or polyspike-and-wave. A diffuse cortical atrophy was detected in 34 patients on neuroimaging. Twenty-seven patients were treated with antiseizure medication (ASM) monotherapy, with reduced seizure frequency in 17 patients. Levetiracetam and valproic acid were the most used ASMs. Up to 41% of patients were unresponsive to first-line treatment and needed adjunctive therapy for seizure control.

Conclusions: AD-related pathological changes in the brain may play a role in LOMEDS onset, although the mechanism underlying this phenomenon is still unknown. EEG remains the most relevant investigation to be performed. A significant percentage of patients developed a first-line ASM refractory epilepsy. ASMs which modulate the glutamatergic system may represent a good therapeutic option.

1. Introduction

Down syndrome (DS), caused by chromosome 21 trisomy, is the most common cause of genetic-related intellectual disability. According to recent epidemiological studies, almost 1 in 400-1500 newborns every year is diagnosed with DS. Individuals with DS may present

Abbreviations: AD, Alzheimer's Disease; ASM, anti-seizure medication; CBZ, carbamazepine; DS, Down Syndrome; CT, computed tomography; EEG, electroencephalogram; GTCS, generalized tonic-clonic seizures; LEV, levetiracetam; LMT, lamotrigine; LOMEDS, late-onset myoclonic epilepsy in Down syndrome; MRI, magnetic resonance imaging; MS, myoclonic seizures; PB, phenobarbital; PER, perampanel; PIR, piracetam; TPM, topiramate; VPA, valproic acid.

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heterogenous clinical pictures, including congenital heart diseases, hypothyroidism, diabetes, obstructive sleep apnea, hearing loss, vision problems, and developmental and behavioral disorders. Several neurological comorbidities can be associated with DS including movement disorders (e.g., myoclonus, parkinsonism, chorea), Alzheimer's Disease (AD), cerebrovascular disease (e.g., Moya-Moya disease), and epilepsy. These disorders are generally observed in the later stage of DS and significantly impact a patient's quality of life and life expectancy [1].

Epilepsy is frequently reported in subjects with DS, with an estimated incidence between 8.1 and 26% [2,3]. It shows a bimodal distribution, with the first peak of incidence in early childhood and the second between the fifth and sixth decade [4]. Epilepsy with generalized myoclonic and tonic-clonic seizures is frequently reported, especially in those patients with an associated severe and progressive cognitive impairment. This peculiar clinical feature has been labeled "late-onset myoclonic epilepsy in Down syndrome" (LOMEDS). LOMEDS exhibits some similarities with other progressive myoclonic epilepsies such as Lafora and Unverricht-Lundborg diseases, characterized by a gradual worsening in antiseizure treatment response and cognitive decline [5]. Diagnosis of LOMEDS is generally based on clinical and instrumental evaluation (e.g., electroencephalogram or magnetic resonance image of the brain) and may be challenging due to various seizure mimics that should be ruled out (e.g., involuntary movements, hallucinations, and cognitive fluctuation).

Seizure freedom can be achieved in more than 80% of LOMEDS cases. Generally, Levetiracetam (LEV) represents the first anti-seizure treatment choice, followed by valproic acid (VPA), whose efficacy has been proven in several population-based studies [6]. Although LEV is usually well tolerated, VPA has been occasionally associated with moderate-to-severe adverse effects, including bradykinesia, resting tremor, rigidity, postural instability, and a wide range of cognitive deficits [7]. Additional therapies may be attempted in the remaining 20% of patients with non-responsiveness to first-line anti-seizure medication (ASM) treatment, albeit no specific recommendations are currently available.[8]

This systematic review summarizes the available information regarding the diagnosis and treatment of LOMEDS, focusing on the efficacy and tolerability of the most largely used ASMs.

2. Methods

2.1. Search strategy, data extraction, and quality assessment

The results of this systematic review were reported according to the statement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA).

We sought the literature for studies that provide data on the diagnostic and therapeutic management of patients with LOMEDS. The following electronic databases and data sources were systematically searched: MEDLINE (accessed through PubMed), EMBASE, and Google Scholar. Searches were carried out from the first available date until August 2022 and followed the strategy reported in Supp.Tab.1.

Seven reviewers (C.C., G.E., S.C., S.C., D.L., G.P., S.M.) independently screened the retrieved articles for possible inclusion. Disagreements were collegially discussed and resolved.

We extracted and collected the following individual patients' data: age, comorbidity (Yes or No), previous diagnosis of epilepsy (Yes or No), diagnosis of dementia (Yes or No), seizure types and frequency, neuroradiological assessment (Magnetic Resonance Imaging, MRI) or Computed Tomography, CT)), electroencephalogram (EEG) findings, ASM treatment, treatment responsiveness, and adverse events. Extracted data were collected on a pre-specified digital spreadsheet. The entire list of variables used for statistical analysis and missing data is reported in Supp.Tab.2.

The quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS)11. According to this scale, each study has been evaluated on the basis of eight items, described as follows: 1) representativeness of the exposed cohort; 2) selection of the not exposed cohort; 3) ascertainment of exposure; 4) demonstration that outcome of interest was not present at the start of the study; 5) comparability of the cohorts included; 6) assessment of outcome; 7) adequate length of the follow-up; 8) adequacy of follow up of cohorts. This score ranges from 0 to 9, and a quality score equal to or higher than three was considered acceptable.

The review protocol was registered in PROSPERO, the international prospective register of systematic review (https://www.crd.york.ac.uk/PROSPERO/, CRD42023390748)

2.2. Statistics

Statistical analysis was performed on the final dataset containing all individual patient data extracted from the included studies. We performed a pooled analysis using descriptive statistics (mean ± SD, frequency) to depict the pooled dataset.

3. Results

3.1. Literature search

The literature search yielded 2753 results (MEDLINE: 170 results; Google Scholar: 1870; EMBASE: 713). Of the 2753 records screened, the full text of 13 articles was reviewed for eligibility. Four articles initially considered for possible inclusion were eventually excluded (excluded articles with reasons for exclusion are reported in Supp. Tab.3). Nine studies (5 case series and 4 case reports) [9–17] fulfilling the selection criteria were finally included (Fig. 1). According to Newcastle-Ottawa Quality Assessment Scale (NOS), one paper reviewed was scored 5, seven papers were scored 4, and one paper was scored 3 (score results in detail are shown in Supp. Table 4).

3.2. Clinical features

We extracted individual data from 46 patients, with a mean age of 48.2 ± 9.2 years (range: 38-69). DS was diagnosed according to the patient's clinical and genetic characteristics. However, specific information regarding genetic tests was reported only in 13 cases (13/46, 28%), with 12 patients presenting a 21-chromosome trisomy in the karyotype (47, XX,+21 or 47,XY,+21) and 1 patient showing a non-balanced 21- chromosome translocation. Twelve patients (12/46, 26%) presented clinical comorbidities, such as heart pathologies (e.g. mitral insufficiency and congenital heart disease), visual system issues (e.g. hypovisus and retinal detachment), or hypothyroidism.

All patients showed a progressive cognitive decline characterized by memory loss, neuropsychiatric symptoms, and progressive loss of ability in activities of daily living. Diagnosis of AD preceded the onset of epilepsy in all cases. The most frequently reported seizure types were myoclonic seizures (MS) (46/46, 100 %) and generalized tonic-clonic seizures (GTCS) (28/46, 61%).

MS occurred at a mean age of 51.3 years and were generally characterized by the predominant involvement of the upper limbs and a subsequent spreading to the head and trunk. Myoclonus was described as positive (i.e., abrupt muscle contraction) or negative (i.e., sudden cessation of ongoing muscular activity) as well as symmetrical or asymmetrical. MS were more frequently reported immediately after awakening or in presence of fatigue. During the course of the disease, 15 patients experienced massive MS, causing frequent falls and, in some cases, hospitalization.

In those patients with GTCS, their occurrence preceded the onset of myoclonic jerks in all cases. Generalized myoclonic-tonic-clonic seizures were described in just one case.

Further neurological signs on neurological examination were reported in 16 patients. The most frequent were impaired speech,

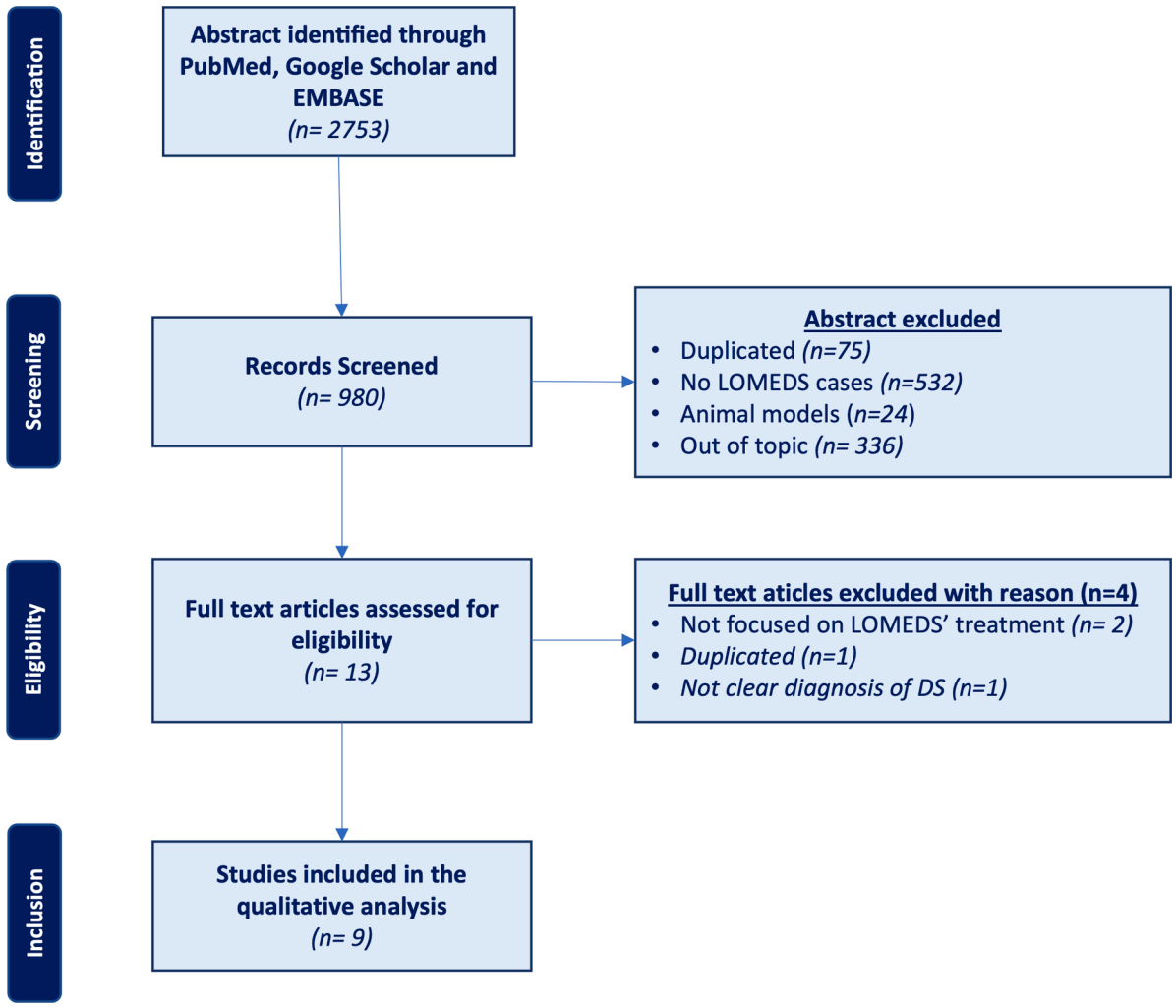

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram describing the search from literature; 980 records were screened from which 9 articles were selected. DS: Down Syndrome; LOMEDS: Late-onset myoclonic epilepsy in Down Syndrome.

cerebellar ataxia, gait disorders, drowsiness, postural instability, hypertonia, and bradykinesia.

No cases of status epilepticus were reported.

Patients' demographics and clinical features are summarized in Table 1. An extended version of patients' single data is available in Supp. Tab.5.

3.3. EEG end neuroimaging

Electroencephalogram (EEG) was performed on 45 patients (45/46, 98%). Patients generally showed diffuse theta/delta slowing associated with diffuse spike-and-wave or polyspike-and-wave bursts, typically upon awakening. A photo paroxysmal response (PPR) was detected in thirteen (13/46, 28%) patients. The EEG features varied with the disease's progression, with a further slowing of background activity associated with increased interictal epileptic discharges.

Neuroimaging data were reported in 34 patients (34/46, 74%). Computed tomography (CT) scan of the brain was performed in almost all patients, whereas magnetic resonance imaging (MRI) scan of the brain just in 3 cases. The main findings were diffuse cortical brain atrophy and ventricle enlargement. Furthermore, two patients exhibited normal radiological findings, while cerebral atrophy was associated with hydrocephalus in one case.

Patients' EEG and neuroimaging features are summarized in Table 1. An extended version of patients' single data is available in Supp.Tab.5.

3.4. ASM treatment and outcome

Monotherapy was administered in 27 cases (27/46, 59 %), resulting in reduced seizure frequency in 17 patients and seizure freedom in two cases. In this context, levetiracetam (LEV) was the most widely used (14/46), followed by valproic acid (10/46), oxcarbazepine (OXC) (1/46), lamotrigine (LMT) (1/46), and perampanel (PER) (1/46, 2%).

ASM polytherapy was employed in 19 cases (19/46, 41%). LEV was administered in association with valproic acid (VPA) in 6 patients, lamotrigine (LMT) in 2 patients, carbamazepine (CBZ) in 3 patients, phenobarbital (PB) in 1 patient, and piracetam (PIR) in 1 patient. On the other hand, VPA was administered in association with topiramate (TPM) in 2 patients and CBZ, LMT, TPM, and PER in 1 patient, respectively. A reduced seizure frequency was reported in 11 patients treated with ASM polytherapy.

Few data were available on adverse events (AE) of ASM treatment, probably due to the shortness of patients' follow-up period. Severe AE were described only in 2 patients and consisted of behavioral disorders in one patient treated with LMT, and bradykinesia in one patient treated with VPA. In both cases, the onset of these AE led to treatment withdrawal or dose adjustment. Mild AE were reported in 2 patients treated with LEV or VPA (both in monotherapy and polytherapy) and consisted of irritability and daily somnolence. A case of irritability due to LMT use was also described. No specific AE were reported in association with PER and TPM.

Table 1
Demographics and clinical features, instrumental findings and ASM treatment strategies in LOMEDS patients.

Study	Total n° of cases (sex)	Age ± SD	Seizure type	EEG	Neuroradiological findings (n° of patients)	ASMs (n° of patients)	Efficacy
G. d'Orsi et al, 2014	12 (7F, 5M)	51.42 ± 7.29	MS, GTCS	Diffuse slowing. Diffuse SW, PSW during awake and sleep. PPR	Cerebral atrophy (11) Hydrocephalus (1)	LEV (7), VPA (1), OXC (1), LMT (1), LEV + CBZ (1), LEV + PB (1)	Responder (reduction SF > 80%)
Crespel A. et al, 2007	2 (1F, 1 M)	52.5 ± 3.54	MS, GTCS	Slow BA, few fast generalized spike-waves only in the awakening period. Diffuse SW and PSW. PPR	Brain cortical atrophy and ventricular enlargement (2)	LEV + LMT LEV + VPA	Responder (not specified SF reduction)
L.M. Li et al, 1995	1 (M)	50	GTCS, MS	Widespread anterior slow activity with occasional intermittent generalised epileptiform discharges	Not available	VPA+ CBZ	Responder (not specified SF reduction)
Moller et al, 2001	1 (M)	55	GMTS, MS	Diffuse slowing, generalized polyspike-and-wave complexes	Cerebral atrophy	VPA + TPM	Responder (not specified SF reduction)
Sangani et al, 2010	2 (2 M)	48 ± 5.66	MS	Slow (6-7 Hz) BA. Generalized intermittent diffuse slowing. MS associated with generalised SW and PSW	Not available	LEV	Responder (seizure freedom)
De Simone et al, 2010	18 (12 F, 6 M)	49.7 ± 6.35	MS, GTCS	Diffuse slowing; generalized slow SW and SSW, PPR	Diffuse atrophy (10) Not available (8)	LEV (2), VPA (6), LEV + LMT (1), LEV+VPA (5), VPA+TPM (1), VPA+ LMT (1), LEV+PIR (1), SCB+PB (1)	Only pooled data information available *["A clear suppression of seizures using VPA was seen in five cases (two with VPA alone). LEV use was successful in five cases (one with LEV alone). TPM, LTG and PIR were used only in combination with LEV, VPA, or phenobarbital (PB) (five patients) with a documented good effect in three cases"]*
Obara et al, 2020	1 (F)	52	MS	Generalized continuous slowing, generalized intermittent rhythmic sharp waves, and generalized PSW	Diffuse atrophy	PER	Responder (seizure freedom)
Corniello et al, 2022	1 (M)	46	MS	Slow (4-5Hz) BA associated with bifrontal high amplitude (100-130 uV) sharp waves	Not available	PER + VPA	Responder (reduction in SF > 75%)
Aller-Alvarez et al, 2014	8 (6 F, 2 M)	45.14 ± 12	MS, GTCS	Diffuse slowing and generalized PSW; left frontotemporal interictal epileptiform abnormalities	Anterior or posterior atrophy and diffuse cortical- subcortical atrophy (8)	VPA (4), LTG (1), CBZ (1), VPA+LEV (1), LEV + CBZ (1)	Only patients treated with two ASMs showed a SF reduction

ASM: anti-seizure medication; BA: background activity; CBZ: carbamazepine; FT: fronto-temporal; GMTS: generalize myoclonic-tonic seizure; GTCS: generalized tonic-clonic seizure; LEV: levetiracetam; LMT: lamotrigine; MS: myoclonic seizure; OXC: oxcarbazepine; PB: phenobarbital; PER: perampanel; PIR: piracetam; PPR: photoparoxysmal response; PSW: polyspike-wave discharges; SCB: sodium channel blocker; SF: seizure frequency; SW: spike-and-wave discharges; TPM: topiramate; VPA: valproic acid.

ASMs treatment strategies are summarized in Table 1. An extended version of single data patients is available in Supp.Tab. 6.

4. Discussion

In the last decades, a relevant increase in the life expectancy of patients with DS has been observed due to the improvement of the clinical management of the disease's complications. Consequently, the prevalence of specific age-related neurological comorbidities, such as epilepsy, has also increased.

As one of the main findings of our analysis, we report that LOMEDS generally occurs in patients with a confirmed diagnosis of Alzheimer's disease (AD). AD in Down Syndrome (AD-DS) is a genetically determined form of AD. It is caused by the overexpression of the amyloid precursor protein (APP) gene located on chromosome 21 which is also involved in the amyloid cascade [18]. The typical neuropathological changes which are observed in AD (i.e., amyloid and phospho-tau cerebral deposition) may play a pivotal role in epileptogenesis [19]. The potential mechanisms have been largely investigated in preclinical APP mouse models for AD. In the early stages of the disease, high levels of amyloid adduct interfere with the reuptake of glutamate or the release of the neurotransmitter from presynaptic terminals, leading to neuronal hyperactivity [20]. Such overactivation is followed by silencing of the affected microcircuit - likely through compensatory inhibitory mechanisms [21] - and, eventually, neuronal death [22]. Further evidence has shown that synaptic dysfunction observed in this condition is associated with an abnormal remodeling of neuronal circuits involving hippocampal-entorhinal areas. In addition, phospho-tau deposition may significantly increase extracellular glutamate, which can promote cellular hyperexcitability [23]. Interestingly, the relationship between amyloid deposition and epileptogenesis is likely bidirectional. If beta-amyloid deposition promotes epileptogenesis, seizures, and interictal epileptiform discharges, recurrence seems to favor beta-amyloid gathering [24]. From the clinical point of view, patients with sporadic AD generally show peculiar focal seizure types, including seizures with automatisms, behavioral arrest, autonomic as well as focal-to-bilateral tonic-clonic seizures [25,26]. On the contrary, MS are less frequently described in these patients and eventually reported in association with presenilin-1 mutation (i.e., a gene implied in the amyloid cascade), as also confirmed in experimental studies [27]. The different seizure semiology observed in sporadic AD and AD-DS may be related to the peculiar brain topography of the AD-related neuropathological

abnormalities. Though AD patients generally present amyloid deposition in the entorhinal cortex, the hippocampus, the parahippocampal region, the amygdala, and the thalamus [28,29], DS patients show these neuropathological changes in frontal and parietal areas [30,31,32] which are involved in motor networks and MS onset [33].

However, the amyloid-related epileptogenic paradigm is not robust, and some criticism has emerged [34]. The most common objection is that, if amyloid deposition played a central role in epilepsy onset, almost all patients with AD would manifest epilepsy as comorbidity. Nevertheless, epidemiological studies show that up to 12.7% of AD patients suffer from epilepsy and this percentage rises to 49.5% in those with early-onset AD [35,36]. Hence, the underlying pathophysiology still needs clarification.

Considering the close link between cognitive decline and LOMEDS onset, a prompt diagnosis of AD in patients with DS is crucial to identify patients who would benefit most from an epileptological evaluation. However, AD diagnosis in DS may be challenging due to the high variability of symptoms (ranging from memory deficits to social withdrawal or aggression) which are not always recognized by the caregivers or misinterpreted as part of lifelong intellectual disability [37]. Indeed, consultations for cognitive decline are often performed when patients already show behavioral disturbances or daily living activities impairment. Therefore, a routine neuropsychological evaluation could be helpful as a specific proactive screening tool to identify the onset of AD, thus recognizing patients at higher risk of LOMEDS occurrence. However, it must be pointed out that we cannot exclude that LOMEDS onset may be also observed independently from AD-DS diagnosis. Indeed, though all included studies support this association, future longitudinal observational studies should focus on LOMEDS' natural history.

From a diagnostic point of view, though LOMEDS diagnosis is clinical, the EEG and the neuroradiological assessment remain the most relevant diagnostic tools. EEG recordings generally show peculiar polyspike and slow-wave complexes synchronous to clinical manifestations. On the other hand, CT/MRI scans usually show diffuse cerebral cortical atrophy.

Different treatment strategies can be attempted in LOMEDS management. According to our data, LEV was the most used ASM, followed by VPA. Several studies have established the efficacy of LEV in myoclonic epilepsies. Furthermore, according to experimental data, treatment with LEV may help modulate those networks involved in behavioral disturbances and memory deficits, leading to amelioration of cognitive performances [38]. Despite its efficacy profile, treatment with LEV may trigger, in the general population, the appearance of somnolence, dizziness, and behavioral and psychiatric disorders (including irritability, hostility, anxiety, apathy, emotional lability, and depression). However, according to our data, LEV administration in patients with LOMEDS was well tolerated in most cases. Indeed, LEV-related psychiatric adverse effects of moderate entity were reported just in one case. Hence, no specific warning should be notified for LEV treatment, although it must be pointed out that the LOMEDS population may be vulnerable to the side effects of all ASMs.

A further therapeutic option in LOMEDS management is VPA. According to our results, VPA showed great efficacy in seizure control through several adverse effects have been reported. In addition, data in the literature stress that VPA should be used with caution in older patients as it can promote brain volume reduction, especially in those patients with a neurodegenerative disease such as AD [39].

Even if ASM monotherapy showed significant efficacy in LOMEDS, our data showed that up to 41% of patients needed adjunctive therapy for seizure control. In this context, sodium channel blockers (SCB) (i.e., CBZ, OXC, and LMT), TPM, and PER are the most frequently employed. SCB add-on therapy was reported in ten patients with no precise details about efficacy and tolerability. It must be pointed out that SCBs are generally not recommended in the management of myoclonic epilepsies given their well-known side effects on myoclonus.

TPM add-on therapy was employed in 2 patients already receiving VPA treatment. This combination showed great therapeutic efficacy. However, the use of TPM in patients with cognitive decline is controversial. TPM may worsen cognitive functioning, and in particular attention, short-term memory, and verbal fluency [40].

Finally, PER use was reported in 2 cases, effectively achieving seizure control. Perampanel is a noncompetitive antagonist of the ionotropic glutamate receptor subtype alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA). Recent studies support the efficacy of PER in the treatment of myoclonic epilepsies [41,42]. Patients with cortical myoclonus generally exhibit hyperexcitability of the cortico-subcortical sensorimotor network. As supported by neurophysiological studies, glutamate is the driver of the phenomenon. Hence, ASM interfering with glutamatergic synapses like PER may show significant therapeutic efficacy in myoclonus control. In addition, the reduction of glutamate-mediated cellular hyperexcitability may also produce positive effects on cognitive functions. Supporting this statement, experimental studies show that the modulation of hyperexcitability ameliorates cognitive performance [43]. To date, no data are available regarding the cognitive effects of PER treatment in elderly patients with epilepsy and dementia though promising results are supported by experimental preclinical data [44]. It must be emphasized that all the available information about LOMEDS treatment comes from case reports and case series, and, to date, no randomized controlled trials have been conducted.

LOMEDS clinical course may be extremely variable with patients presenting well-controlled epilepsy as well as patients with MS which become progressively more frequent and severe, thereby producing recurrent body trauma. The increased seizure burden and the occurrence of drug-resistant epilepsy, along with the worsening of cognitive performance, significantly impact the patient's quality of life. Furthermore, a higher incidence of sudden unexpected death in epilepsy (SUDEP) is generally reported in drug-resistant epilepsy [45–47].

5. Conclusion

LOMEDS' onset is usually related to the later stages of DS. MRI and EEG may be helpful in the diagnosis. Treatment of LOMEDS may represent a challenge and should always consider the patient's cognitive and psychiatric profile. More extensive multicenter observational studies are required to define the most adequate therapeutic strategies.

Declaration of Competing Interest

Authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.05.017.

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