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Review

Diagnosis and treatment of status epilepticus in Down Syndrome (DS): A case report and systematic literature review

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ABSTRACT

Introduction: Epilepsy is one of the most frequent neurological comorbidities in patients with Down Syndrome (DS). Young patients and adults are the most affected, the latter mostly showing a phenotype labeled as "Late-onset myoclonic epilepsy" (LOMEDS). Status epilepticus (SE) is a life-threatening complication in patients with epilepsy. In this study, we described a non-convulsive SE (NCSE) case in a patient diagnosed with LOMEDS. We also performed a systematic review of the literature on SE diagnosis and treatment in patients with Down Syndrome.

Methods: Clinical and demographic characteristics of a DS patient diagnosed with NCSE were described. The systematic literature search dissected the diagnostic and therapeutic management of SE in patients with DS. The following databases were used: PubMed, EMBASE, and Google Scholar.

Results: 5 DS individuals (4 from the past literature + 1 novel case report) with SE have been identified. The median age at SE onset was 42 years (IQR: 21–60.5 years). The most common SE type was myoclonic SE (MSE), followed by NCSE. Two cases of acute symptomatic etiology were described, whereas a progressive symptomatic etiology was otherwise reported. Ictal EEG recording information was available in two patients who showed generalized spike waves and polyspike and wave discharges. In 3 cases, SE was treated with intravenous anti-seizure medications that produced a complete resolution.

Conclusion: SE may represent a rare complication in patients with DS. Although no definitive conclusions may be achieved due to the lack of evidence, treatment with valproic acid seems effective, especially in MSE. NCSE management is more challenging. It requires low doses of anesthetics, which should be used cautiously due to the high rate of complications.

1. Introduction

Down Syndrome (DS) is the most frequent genetic-based cause of intellectual disability all over the world. DS can be caused by trisomy of chromosome 21 as well as balanced or non-balanced translocation involving the same chromosome [1]. Neurological comorbidities are frequently reported in individuals with DS, among which epilepsy is one of the most reported, accounting for about 26 % of all affected individuals [2].

In patients with DS, epilepsy diagnosis may be ascertained during all ages, though the first years of life and later adulthood are the most frequent. Adults may present a peculiar picture characterized by frequent generalized tonic-clonic and myoclonic seizures, labeled as "Late onset myoclonic epilepsy in Down Syndrome'' (LOMEDS). LOMEDS is mainly observed in patients presenting cognitive impairment linked to Alzheimer's dementia (AD) and is sometimes associated with a progressive decline in antiseizure treatment response [3].

Status epilepticus (SE) is a life-threatening neurological emergency with high morbidity and mortality, requiring prompt diagnosis and treatment [4]. SE results from the failure of seizure termination or the

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alteration of mechanisms that generate prolonged seizures. Depending on the type and duration of seizures, it is usually associated with long-term sequelae, including neuronal death, neuronal injury, and alteration of neuronal networks [5]. According to the International League Against Epilepsy (ILAE), SE may be classified as with or without prominent motor symptoms and can be defined as refractory when first- and second-line treatments (i.e., benzodiazepine and antiseizure medications) fail.

In this paper, we describe a case of non-convulsive status epilepticus (NCSE) in a patient diagnosed with LOMEDS. Furthermore, a literature review was performed to better characterize the clinical features, treatment strategies, and prognosis of SE with DS.

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). A comprehensive systematic review of the available literature was conducted, searching for case reports and case series on SE in individuals with DS. The following research syntax was employed: [("Down syndrome")/OR ("Trisomy 21″)] AND [("status epilepticus")/OR ("status")/OR ("prolonged seizures")]. The following electronic databases and data sources were systematically searched: MEDLINE (accessed through PubMed), EMBASE, and Google Scholar.

Three reviewers (C.C., F.D., G.E.) independently screened the retrieved articles for inclusion. Disagreements were collegially discussed

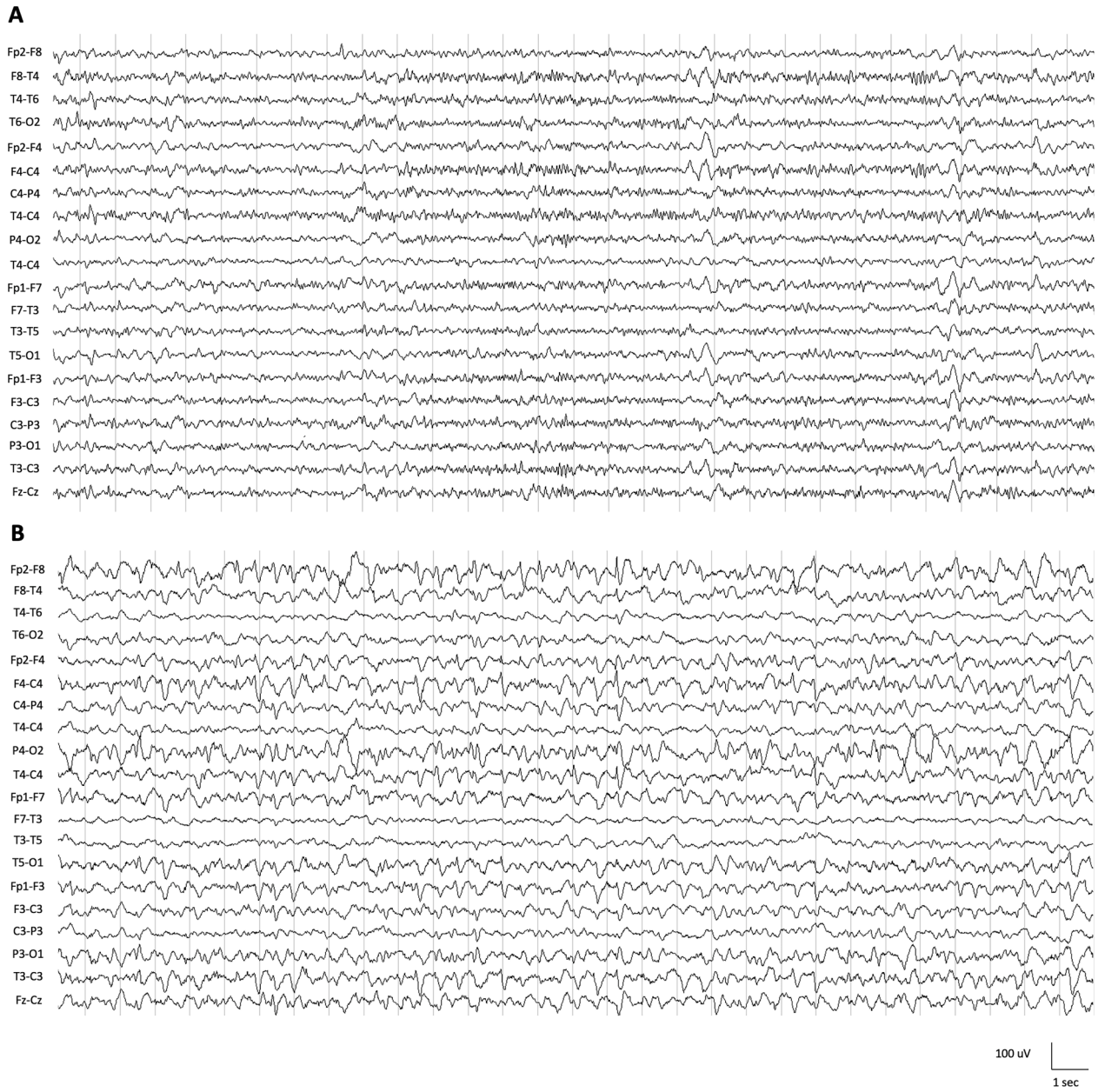

Fig. 1. Electroencephalogram (EEG) recordings performed before (A), and at SE diagnosis (B). (A) 8–9 Hz background activity with sporadic superimposed middle-amplitude (100–150 uV) diphasic sharp waves predominant in the frontal regions; (B) diffuse slowing of the background activity (4–5 Hz) in association with diffuse (right fronto-temporal predominant) diphasic and triphasic sharp waves as well as spike-wave complexes of medium and high amplitudes (100–150 uV), with a maximum frequency of 1–1,5 Hz.

and resolved through discussion. We extracted and collected the following individual patients' data: age, previous diagnosis of epilepsy (Yes or No), SE semiology, SE etiology, electroencephalogram (EEG) findings, SE treatment, treatment responsiveness, SE outcome, STESS (the Status Epilepticus Severity Score) and EMSE-EACE (the Epidemiology-based Mortality score in SE). STESS and EMSE-EACE represent two clinical scoring systems used for outcome prediction in patients with SE. Values of STESS $\geq$ 4 and EMSE-EACE $\geq$ 64 predict a higher risk of death after a SE episode. Extracted data were collected on a pre-specified digital spreadsheet.

The quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) [6,7]. This score ranges from 0 to 9, with studies scoring above 5 evaluated as of good quality.

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 $\pm$ SD, frequency) to depict the pooled dataset.

3. Results

3.1. Case report

A 44-year-old woman was admitted to the emergency room due to the abrupt onset of cognitive-motor impairment associated with subtle and irregular parcel movements of the upper limbs. The patient's past

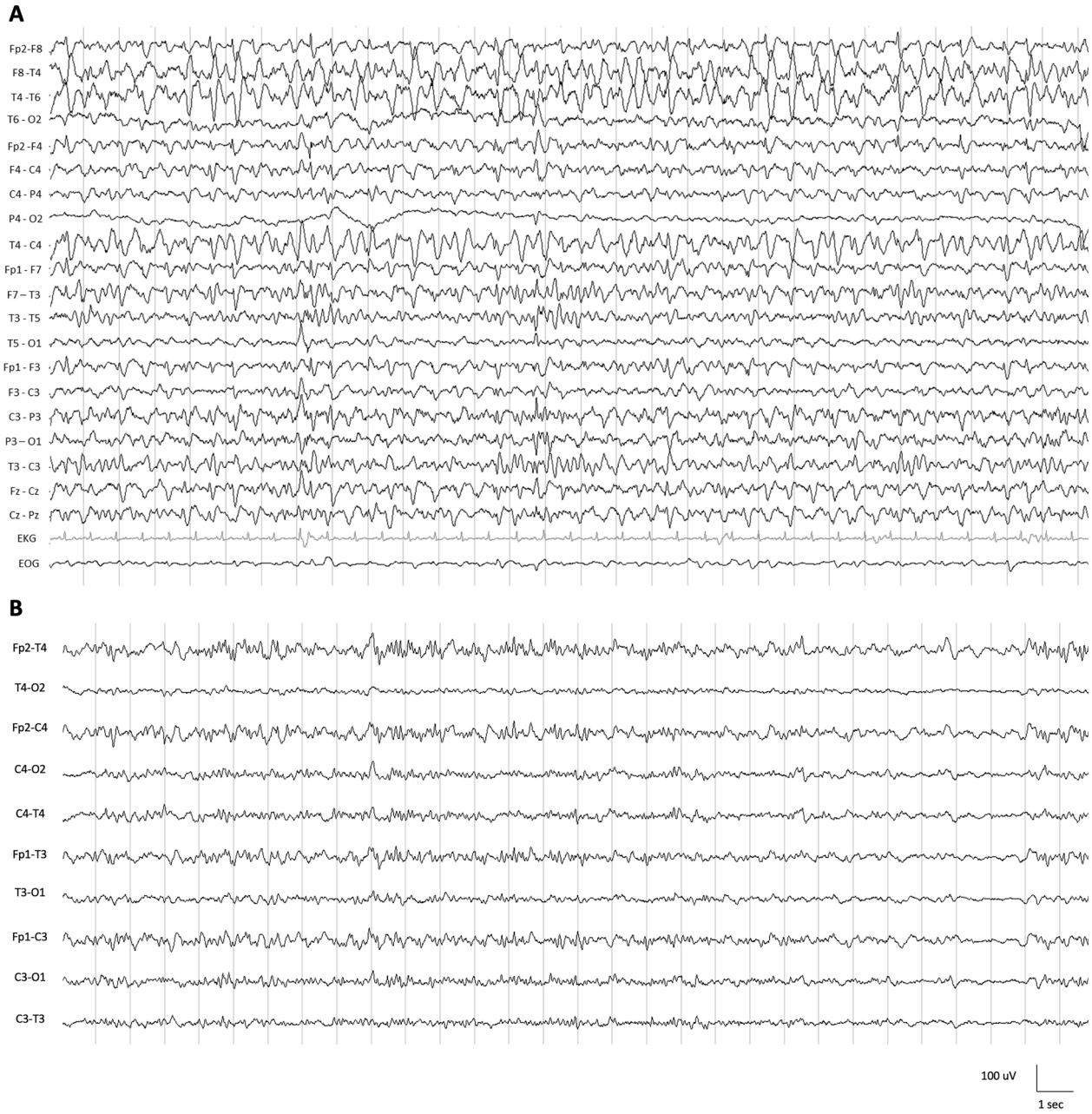

Fig. 2. Electroencephalogram (EEG) recordings performed concomitantly the appearance of oromandibular clonic movements (A), and at SE termination (B). (A) 4–5 Hz background activity with superimposed quasi-periodic right fronto-temporal predominant di- and triphasic sharp waves, of medium and high amplitudes (100–150 uV), with a maximum frequency of 1 Hz; (B) 8–9 Hz background activity with sporadic superimposed middle-amplitude (100–150 uV) diphasic sharp waves predominant in the frontal regions.

medical history included a diagnosis of Down Syndrome (21-chromosome trisomy; karyotype: 47, XX, +21) with the development of Alzheimer's Dementia at the age of 40, followed by LOMEDS onset two years later. The patient was treated with levetiracetam (LEV) 2000 mg/die and eslicarbazepine (ECB) 800 mg/die with a discrete control on seizure frequency. Her last electroencephalogram (EEG) recording, performed 6 months before the admission, showed normal (8–9 Hz) background activity with sporadic superimposed middle-amplitude (100–150 uV) diphasic sharp waves predominant in the frontal regions (Fig. 1A).

At first, the patient underwent a brain CT scan, which showed diffuse cortical atrophy and cerebral ventricles enlargement. An EEG was then performed, which showed a diffuse slowing of the background activity (4–5 Hz) in association with diffuse (right fronto-temporal predominant) diphasic and triphasic sharp waves as well as spike-wave complexes of medium and high amplitudes (100–150 uV), with a maximum frequency of 1–1,5 Hz (Fig. 1B). According to the Salzburg Criteria [9], a diagnosis of non-convulsive Status Epilepticus (NCSE) with subtle motor components was made. Unfortunately, a concomitant pneumonia associated with low blood oxygen level contraindicated the use of benzodiazepine as SE first-line treatment. Thus, the patient was treated with an intravenous (i.v.) bolus of Valproic Acid 800 mg that failed to produce clinical or EEG improvements. Due to the worsening of the respiratory condition, the patient was transferred to the intensive care unit (ICU), where she was intubated and treated with VPA 400 mg bid and a low dose of propofol (0.5 mg/kg/h). Propofol dosage was adjusted according to the patient's hemodynamic characteristics. After 24 h, a first attempt of anesthetic withdrawal was made. At the neurological evaluation, the patient appeared comatose, only able to localize pain (Glasgow Coma Scale, GCS: 5). In addition, subtle parcel oromandibular clonic movements appeared. A new EEG recording showed a slow 4–5 Hz background activity with superimposed quasi-periodic right fronto-temporal predominant di- and triphasic sharp waves of medium and high amplitudes (100–150 uV), with a maximum frequency of 1 Hz (Fig. 2A). The Status Epilepticus Severity Score and the Epidemiology-based Mortality score in SE were calculated, resulting in a score of 4 and 65, respectively, indicating a case of SE associated with a severe risk of mortality. In the following days, the antiseizure medications (ASMs) were progressively modified as follows: LEV 2500 mg/die, VPA 1200 mg, and ESL 400 mg/die associated with propofol (0.5 mg/kg/h), resulting in SE in a resolution after 10 days (Fig. 2B). No additional ASMs were administered. EEG abnormalities and the oromandibular movements completely disappeared.

After 53 days in the ICU, due to the general condition improvement, the patient was transferred to a sub-intensive care unit and then to a rehabilitation clinic. The patient was alert and collaborative at discharge, but severe dysphagia and reduced general motor functioning were reported.

3.2. Literature search

The search strategy yielded 533 results (MEDLINE: 12 results; Google Scholar: 521). After reading the titles and the abstracts, 2 articles (one case series and one case report) were included, with a total of 4 individuals with DS diagnosed with SE [8,9] (Fig. 3). According to NOS evaluation, both articles were scored 4 (Supp. Tab.1). Excluded articles

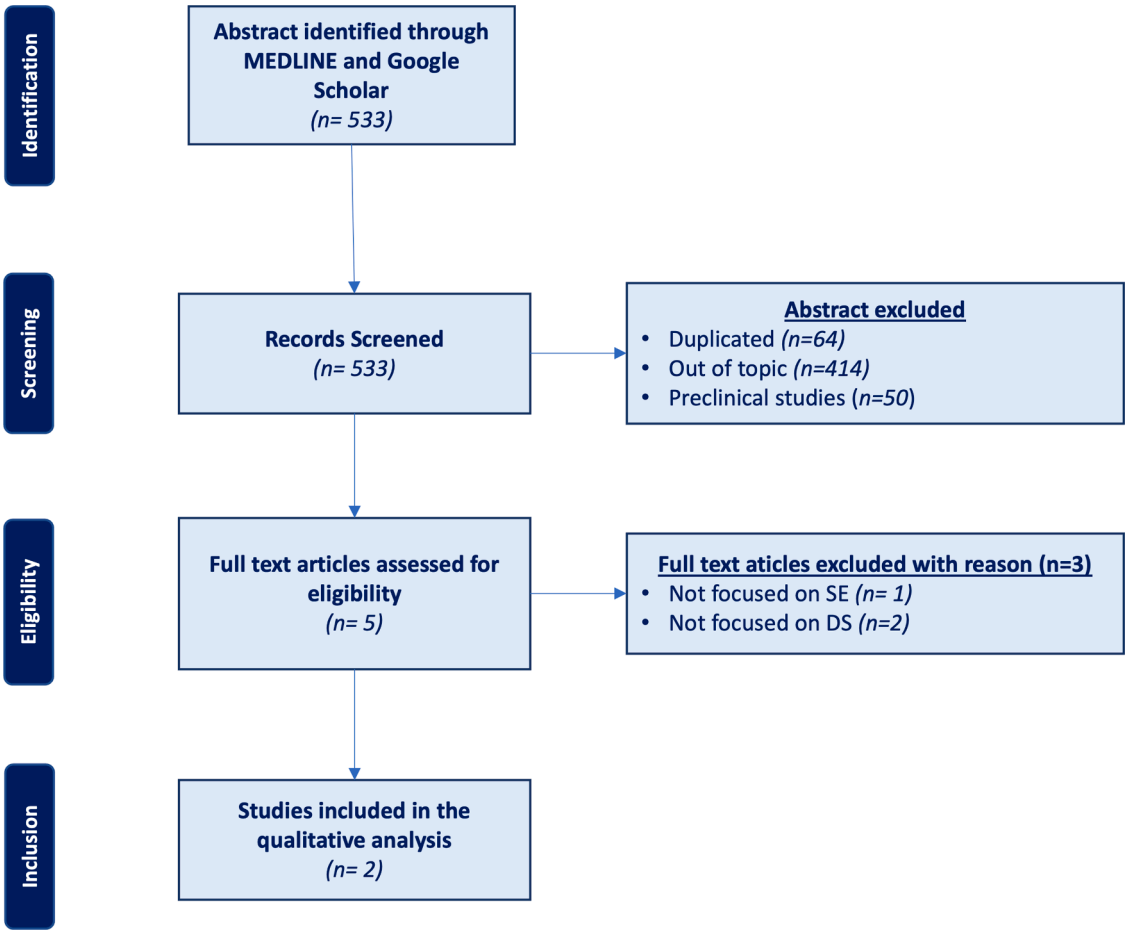

Fig. 3. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram describing the search from literature; 533 records were screened from which 2 articles were selected. DS: Down Syndrome; SE: Status Epilepticus.

and criteria for exclusion are reported in Supp. Tab.2.

The median age at SE onset was 42 years (IQR: 21–60.5 years). According to the past epileptological history, two patients were first diagnosed as LOMEDS. In contrast, in another case, a recurrent history of generalized tonic-clonic seizures associated with eyelid myoclonia was reported. The most common SE type was myoclonic SE (MSE), which occurred in three patients (3/4, 75 %). No clear data about SE type was available in the fourth case. An acute symptomatic etiology characterized by infectious disease (measles infection) was described in one case. Differently, a progressive symptomatic etiology was observed in the other cases. New onset SE was diagnosed in just two patients.

Ictal EEG recording information was available in just one case, showing generalized spike waves and polyspike and slow waves.

SE treatment strategy was reported in two cases, consisting of i.v. VPA administration.

No data about the STESS, EMSE-EACE, and SE outcome was available. Otherwise, a history of progressive cognitive decline was reported in all patients.

Demographics and clinical data of patients are reported in Table 1.

4. Discussion

SE is a life-threatening event in patients with chronic neurological diseases. Our data indicate that DS patients generally develop SE during the later ages of life, along with cognitive decline mostly due to AD. However, the prevalence of this complication is not high in this cohort, almost overlapping with data related to patients suffering from sporadic forms of AD [11]. From the semiological point of view, just myoclonic and non-convulsive SE types have been described. Generally, SE semiologies may vary depending on the underlying etiological causes and the patient's age [12]. In patients suffering from neurodegenerative diseases, NCSE, as well as myoclonic SE, have been reported but without a clear predominance over other SE types [9]. Patients with LOMEDS may express more frequently a myoclonic SE. However, the absence of reports does not allow the possibility to reach definitive conclusions on the predominant SE semiology in DS patients. According to the etiological classification [13], a SE acute symptomatic cause has been reported in 50 % of patients with DS. Systemic infections with fever and no direct central nervous system involvement are the leading cause of SE onset. In the remaining cases, SE etiology remained unknown or, at best, categorizable as progressive due to the underlying neurodegeneration. Preclinical APP models have helped explore the role of amyloid and phospho-tau cerebral deposits in epileptogenesis [14]. High amounts of amyloid impair glutamate reuptake or release from presynaptic terminals in the early stages of the disease, thereby promoting neuronal hyperexcitability [15]. Experimental evidence also indicates synaptic dysfunction that generates aberrant remodeling of neuronal circuits involving the hippocampal-entorhinal regions. Extracellular glutamate levels and hyperexcitability can also be affected by phospho-tau accumulation [16].

SE treatment follows a stepwise therapeutic approach. Generally, i.v. benzodiazepines (i.e., lorazepam, diazepam, and midazolam) are the first line SE treatment [17]. However, due to possible systemic complications, including pulmonary diseases, the use of BDZ may be forbidden. In these cases, straightforward use of i.v. ASMs is generally recommended. According to the latest evidence, LEV, VPA, and PHT are equally effective in treating SE [18]. However, in myoclonic SE, the use of VPA and LEV is encouraged, given the worsening of myoclonus with sodium channel blockers (e.g., PHT). Consistent with these data, our results support the benefits of VPA and LEV in the management of SE in patients with DS, even when administered as first-line treatment. However, BDZ should not be routinely avoided in patients with DS and SE. In our case, the choice of skipping to second-line treatment was driven by the patient's systemic complications (i.e., severe pneumonia and low blood oxygen levels). In contrast, in the other cases described in the literature, no major explanations have been provided to justify this therapeutic approach. After the failure of the second-line ASM treatment, about 31–43 % of patients generally require i.v. anesthetics (i.e., thiopental/pentobarbital, midazolam, or propofol) [19] for SE. However, anesthetic drugs are usually associated with several adverse events, including a high rate of systemic infections and death. Midazolam infusion may cause respiratory depression, hypotension, and non-anion gap hyperchloremic metabolic acidosis [20]. On the other hand, propofol infusion syndrome, characterized by metabolic acidosis, cardiac failure, bradycardia, hypertriglyceridemia, hepatotoxicity, rhabdomyolysis, and renal failure, can be observed with the use of higher dose (>4 mg/kg/h) and longer duration (>48 h) therapy [21]. Individuals with DS seem to be particularly at risk of cardiovascular complications and decreased SpO2 during i.v. sedation, especially after administering higher doses of propofol in combination with midazolam [22]. Sleep apnoea, upper-airway obstruction due to a large tongue, and concomitant congenital heart disease are possible risk factors determining a worse outcome. Similarly, DS patients undergoing i.v. sedation with midazolam exhibit prolonged recovery time [22]. Therefore, these patients need close and comprehensive monitoring during anesthetics administration.

5. Conclusions

SE is a rare but life-threatening complication in DS patients. Older patients are more vulnerable to SE, though no major conclusions about age-related risks can be reached due to the lack of a sizeable number of reports. VPA treatment is generally employed in SE management with successful results. Third-line therapy should be administered with caution.

Statement of ethics

Written informed consent was obtained from the caregiver for the publication of this case report and any accompanying images. The paper is exempt from ethical committee approval because it is not necessary for the publication of the case report. We confirm that we have read the

Table 1
Demographics, clinical and instrumental findings in DS patients with status epilepticus. MSE: myoclonic status epilepticus; NA: not available; SE: status epilepticus; STESS: Status Epilepticus Severity Score; VPA: valproic acid.

Study	Total n° of cases	Sex	Age	SE semeiology	SE aetiology	EEG	SE treatment	Treatment responsiveness	Outcome
Takasugi et al. [8]	1	M	2	NA	Acute symptomatic (measles infection)	NA	NA	SE resolved	Multiple cerebral infarction (Moya-Moya syndrome)
Vignoli et al. [10]	3	M	49	MSE	Progressive symptomatic	NA	VPA (2/3 patients)	SE resolved	Cognitive decline
		F	59	MSE		NA			Cognitive decline
		F	40	MSE	Progressive symptomatic Progressive symptomatic	Spike-waves and polyspike-waves			Cognitive decline

Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Author contributions

CC and FD contributed to the conceptualization and design of the study. CC, FD, GE, and SLS wrote the manuscript. All authors contributed to the review and editing of the manuscript, and read and approved the submitted version.

Data availability statement

The data are available from the corresponding author upon reasonable request.

Declaration of Competing Interest

The authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.11.009.

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