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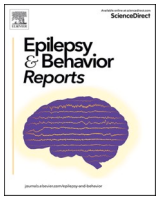

Stroke-related epilepsy in the rehabilitation setting: Insights from the inpatient post-stroke rehabilitation study – RIPS

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ABSTRACT

In stroke survivors, persistent seizure activity could be associated with poor functional outcomes. At the same time, antiepileptic over-treatment could hamper post-stroke recovery. We systematically investigated the occurrence of seizures, the prevalence of epileptic discharges, and delta slow waves on electroencephalogram (EEG) and anti-seizure medication (ASM) management in relation to clinical manifestations and EEG abnormalities. This was a multi-centre prospective study involving two intensive rehabilitation units (IRUs). Clinical and EEG data were acquired at admission to the IRU, discharge (T1), and six-month follow-up (T2). A total of 163 patients underwent EEG recording upon admission to the IRU, while 149 were available for analysis at discharge from the IRU. Eighteen patients were treated with ASMs upon IRU admission despite only five of these patients having early seizures. Among the 145 patients not treated upon admission to the IRU, eight had late seizures, of which six were during the IRU stay, while two were after discharge from the IRU. During IRU stay, ASMs were generally discontinued in patients with no early seizures reported and were started in patients with late seizures. Among the 18 patients treated with ASMs at admission to the IRU, only six maintained the therapy also at T2. Our results suggest that post-acute inpatient rehabilitation is a proper setting to observe patients treated with ASMs after stroke and provide personalized post-stroke epilepsy management.

1. Introduction

Stroke-related epilepsy (STRE) [1] ranges from 2 % to 14 % depending on the study population [2,3] and accounts for nearly 50 % of newly diagnosed epilepsy inpatients over 60 years old. With the increasing prevalence of post-stroke survivors, mainly related to the aging of the population and the improvement of hyperacute stroke care, the number of patients with STRE is expected to increase [4,5]. Seizures may occur in close temporal association with stroke (acute symptomatic, provoked, or early seizures (ESs), or after a variable interval, from several days to years following the stroke (late seizures, LSs) [6]. While ESs result from local metabolic disturbances, LSs occur in relation to altered neuronal networks, i.e. when the brain acquires a predisposition for seizures. In stroke survivors, persistent seizure activity could hamper post-stroke recovery, cause temporary or even permanent neurological deterioration, and predict poor functional outcomes [7]. Furthermore, seizures affect not only the quality of life of the patient but also that of their families [8]. STRE may occur or recur during post-acute rehabilitation [9]. Therefore, the management of LSs should be considered as part of the individual rehabilitation project, aiming to improve functional outcomes in post-stroke patients with STRE. Specifically, STRE diagnosis and the management of anti-seizure medication (ASM), mainly based on careful evaluation of efficacy combined with the evaluation of side effects and drug-drug interaction, are a necessary intervention to be carried out during the rehabilitation stay [10].

To the best of our knowledge, the incidence of STRE and ASM management in post-acute stroke inpatient rehabilitation, although relevant to aiming to identify any clinical/instrumental indicators for

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the development of LSs and to improve the management of post-stroke patients in a sub-acute setting, has not been investigated by previous studies. Thus, in the context of a multicentre observational prospective study investigating predictors of functional outcomes at discharge from inpatient post-stroke rehabilitation (RIPS study) [11], we aimed to systematically observe the occurrence of early and late seizures, from admission to the Intensive Rehabilitation Unit (IRU) to discharge and to six-month after the stroke and the relationship between seizure and the prevalence of epileptic discharges, and delta slow waves on the electroencephalogram (EEG) In addition, we aimed to describe and discuss ASM management in relation to clinical manifestations and EEG abnormalities.

2. Material and methods

2.1. Study design

Data analysed in the current paper were obtained from the RIPS study [11]. This work involved two Intensive Rehabilitation Units (IRUs) of Fondazione Don Carlo Gnocchi (Firenze, La Spezia) out of the four IRUs participating in the RIPS study. All subjects admitted to either of the two IRUs since December 2019 were systematically assessed for eligibility and recruited. Inclusion criteria were (1) adults (age $\geq$ 18 years); (2) presenting first-ever ischemic or haemorrhagic stroke, diagnosed both clinically and through brain imaging; (3) index acute event onset within 30 days or less. Patients were excluded from the study if they had epilepsy before their stroke [12]· Stroke patients admitted to the severe acquired brain injuries intensive ward because of severe disorders of consciousness state or critical clinical conditions due to severe haemorrhagic or ischemic strokes were not included in this study. Participants' clinical and demographic features were collected through interviews or retrieved from clinical records.

Brain-computer tomography was classified according to the Oxfordshire Community Stroke Project classification when ischemic aetiology is considered [13]. Seizures were considered as early (ESs) or late (LSs) according to the interval between stroke onset and seizure presentation. Unprovoked seizures occurring more than one week after the stroke were defined as LSs [1]. The ASM prescription for each patient was investigated. Clinical and instrumental data were collected at the following three time points: (1) IRU admission, (T0); (2) discharge from the IRU (T1), and (3) six months after the stroke (T2).

Informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committees of each centre (Firenze: 14513; La Spezia: 294/2019; Massa-Fivizzano: 68013/2019) and was a priori registered on ClinicalTrials.gov (registration number: NCT03968627).

2.2. EEG recordings and classification

Standard EEG was carried out on a chair or a wheelchair based on the patient's clinical condition. During the 20-minute recording period, patient reactivity was assessed through active or passive eye-opening and closing, depending on the degree of the patient's collaboration. Hyperventilation was not performed, as most stroke patients have contraindications arising from age, cardiac, and respiratory problems associated with the cerebrovascular insult [14]. EEG was classified by two of the authors (MS and AG) according to the American Clinical Neurophysiology Society's standardised critical care EEG terminology [15,16]. Epileptic discharges were classified as follows: (1) interictal epileptic activity, (2) periodic discharges, and (3) electric seizures.

2.3. Statistical analysis

All statistical analyses were performed using SPSS software (vs28.0; SPSS Inc). First, descriptive analyses were provided through mean and standard deviation, or median and interquartile range with non-normal distributions, for numerical variables. The frequencies of the group were provided for categorical variables. The normality of the distributions was evaluated with the Shapiro–Wilk test, and for all the tests, a significant result was obtained with a p-value < 0.05.

3. Results

Patients were admitted to either of the two IRUs between December 2019 and January 2021. Among the 278 patients screened for the RIPS study (Fig. 1), 234 were enrolled, 163 (68 %) underwent EEG recording upon admission to the IRU, and 149 were available for analysis at discharge from the IRU. EEG abnormalities were present in 94/163 (57.65) of admitted patients.

Seventy-two (44 %) patients underwent a follow-up visit as outpatients, including a structured clinical and functional assessment and an EEG recording, while 39 patients were evaluated by telephonic interview. The main characteristics of the sample are shown in Table 1. No deaths related to PSE were reported. An overview of LS recurrence, the specific ASM treatments, and EEG patterns upon admission to the IRU are provided in Table 2 and Fig. 2.

3.1. ASM treatment at admission and discharge

Upon admission to the IRU, 18 post-stroke patients were treated with ASM, of which 5 (27.8 %) had ESs. For each patient, EEG abnormalities (Table 2) and eventual change of ASM (Fig. 2) were analyzed at any given time point. In all five patients with reported ESs, EEG abnormalities were detected upon admission to the IRU. In particular, in one patient, with epileptic discharges and delta slow waves on the EEG, seizures were no longer observed. The patient died during the IRU stay, before time T1. In two patients, one with epileptic discharges and one with delta slow waves on the EEG, LSs were reported only during the IRU stay. In both these patients, ASM (levetiracetam associated with phenytoin in one case and with valproic acid in the other one) was reported at admission and it was not modified during the IRU stay. In the remaining two patients, one with delta slow waves and one with an association between epileptic discharges and delta slow waves on the admission EEG, LSs were reported both during the IRU stay and between T1 and T2. Both patients were treated with levetiracetam at all time frames. Among the thirteen patients with ASM, but with no report of ESs, six showed delta slow abnormalities on the EEG, while none showed epileptic discharges. Of these thirteen patients, four presented LSs during the IRU stay (two of them with delta slow EEG abnormalities). However, no epileptic seizure recurrence was reported at T1–T2. Both patients with delta slow EEG abnormalities on the admission EEG were treated with lacosamide and levetiracetam, respectively, both at T0 and T1, while no ASM was reported at the six-month follow-up. Two patients with normal EEG at IRU admission were treated with ASM. One was treated with levetiracetam at T0 and T1 and then discontinued in time frame T1–T2. In the other one, the association of lamotrigine and carbamazepine was reported upon admission to the IRU, but carbamazepine was discontinued during the IRU stay, while lamotrigine was reported both at T1 and T2. Among the remaining nine patients with ASM medication upon IRU admission, four of them had delta slow-wave EEG abnormalities, and no one had epileptic seizures during the IRU stay. ASM treatment was discontinued in all of them, except for one patient with normal EEG, for whom treatment with levetiracetam was continued both at T1 and T2.

ESs were not reported in any of the untreated patients. In 83/145 (57.2 %) patients, EEG abnormalities were reported upon admission to the IRU, including two epileptic discharges, 73 delta slow waves, and eight with both EEG abnormalities.

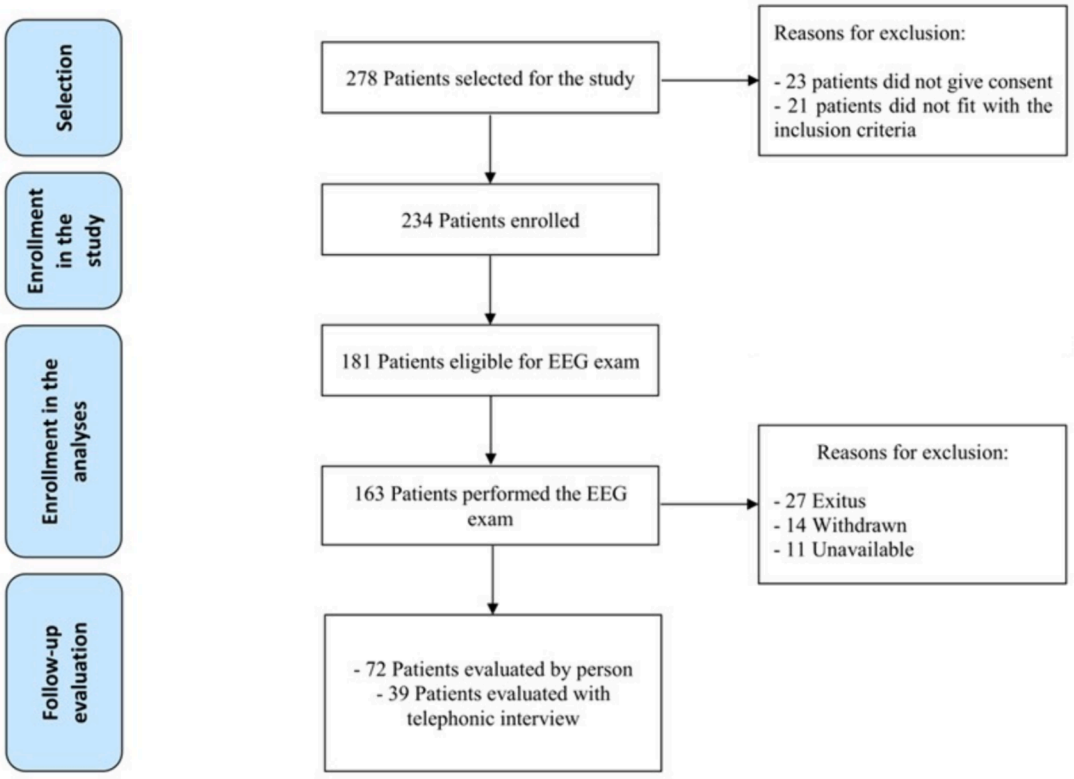

Fig. 1. Flow chart representing the number of patients enrolled in the study and in the analyses.

3.2. Late seizures

LSs were documented in 8/145 (5.5 %) patients. In particular, six patients experienced seizures exclusively during the IRU stay, with no subsequent recurrence reported at T1–T2 (one patient died before the follow-up period). Conversely, two patients exhibited LSs exclusively between time frames T1–T2. Of the eight patients who presented with LSs, two, both with LSs occurring during the IRU stay, exhibited an association of epileptic discharges and delta slow waves, while the remaining six displayed only delta slow-wave EEG abnormalities. In three of the six patients who presented with LSs during the IRU stay, ASM treatment was initiated and maintained until T1. In particular, one patient was initiated on levetiracetam, another was commenced on a combination of levetiracetam and lacosamide, and a third was initiated on clonazepam. Except for the patient who had been taking clonazepam, who died before T2, the ASM treatments reported at T2 remained unchanged. Concerning the two patients in whom LSs were reported only after discharge from the IRU, only one patient received ASM treatment with levetiracetam at T2.

3.3. ASM treatment

Globally, the number of patients with ASM treatment was reduced from 17 (10.4 %) at T0, to 12 (of whom 3 underwent ASM treatment for the first time during the IRU stay) (8.1 %) at T1, and 8 (of whom one patient started the treatment during the time-frame T1–T2) (7.2 %) at T2.

At the IRU admission, ASMs were present in monotherapy in eleven patients, and in association in six patients. At T2, only eight patients were still treated with ASM, 5 in monotherapy, and three by associating two drugs. Compared to the admission, when eight different ASMs were used, only five different ASMs (levetiracetam, lacosamide, phenytoin, lamotrigine, and valproic acid) were reported at the 6-month follow-up (T2). Among these, levetiracetam was the most used medication (in 75 % of patients), both in monotherapy and in association with other ASMs.

4. Discussion

Stroke and epilepsy negatively affect activities of daily living, cognitive function, and quality of life; thus, the contemporary presence of both disorders in the same subject can be devastating [17,18].

Despite the potential for PSE to complicate post-acute inpatient rehabilitation following a stroke, the incidence and management of this phenomenon in this particular context remain poorly described.

In our sample, we observed a few patients with ESs (5.3 %), a value that was in the wide range (2 %–20 %) previously reported in the literature [19–21]. This variability mainly reflects the heterogeneity in different study cohorts regarding stroke aetiology, length of follow-up, definitions of ESs and LSs, and the absence of standard protocols.

We observed a greater number of patients admitted to the IRU with an ASM treatment, revealing the use of many different molecules sometimes associated. The discrepancy between the occurrence of ESs and the presence of an ASM treatment and heterogeneity in the use of different molecules could probably be due to the inhomogeneity in the ASM management of the referring hospital departments. Indeed, the recruited patients came from at least seven different hospitals in the territory of the two rehabilitation centres involved in the current study. In addition, not all patients treated with ASM in the acute phase had an EEG performed, and this may have introduced a high variability in the criteria for the initiation of an ASM treatment.

Moreover, in this prospective observational study, the majority of elements pertaining to the rehabilitation protocol were delineated before the commencement of the study. However, despite the intervention being part of the rehabilitation programme, no specific protocol was agreed upon in advance for the management of seizures. This was due to the absence of reports in the literature investigating both the incidence of seizures and ASM management in post-stroke patients within the temporal window of the rehabilitation phase, resulting in a

Table 1
Demographic characteristics of the sample at T0.

Variable	Overall descriptive: median [IQR] or frequency
Age (years)	80.0 [71.0–85.0]
Gender (Male; Female)	86 (52.8 %); 77 (47.2 %)
Etiology	Ischemic: 129 (79.1 %); Hemorrhagic: 34 (20.9 %)
Oxfordshire Community Stroke Project	LACI: 20 (15.5 %) POCI: 17 (13.2 %) TACI: 14 (10.9 %) PACI: 78 (60.5 %)
Hemorrhagic specification	Intraparenchymal: 27 (79.4 %) Amyloid angiopathy: 2 (5.9 %) Ruptured Aneurysm: 3 (8.8 %) Arteriovenous Malformation: 2 (5.9 %)
Systemic thrombolysis	36 (22.1 %)
Modified Barthel Index total score	33.0 [11.0–57.0]
Modified Barthel Index dependency level	Total (score 0–24): 69 (42.3 %) Severe (score 25–49): 43 (26.4 %) Moderate (score 50–74): 26 (16.0 %) Mild (score 75–90): 13 (8.0 %); Minimal or absent (score 91–100): 9 (5.5 %)
Modified Rankin Score	0: 3 (2.0 %) 1: 3 (2.0 %) 2: 12 (7.8 %) 3: 21 (13.7 %) 4: 88 (57.5 %) 5: 26 (17.0 %)
National Institute of Health Stroke Scale total score	7.0 [3.0–12.0]
National Institute of Health Stroke Scale severity level	Very severe (score 25–42): 2 (1.2 %) Severe (score 15–24): 21 (12.9 %) Mild to moderate severe (score 6–14): 75 (46.0 %) Mild (score 0–5): 64 (39.3 %)
EEG epileptic discharges	3 (2.0 %)
EEG delta slow wave activity	81 (49.8 %)
EEG delta slow wavs and epileptic discharges	10 (6 %)
Side of the lesion	Right: 73 (44.8 %) Left: 79 (48.5 %) Bilateral: 11 (6.7 %)
Area of the lesion	Supratentorial: 136 (83.4 %) Subtentorial: 21 (12.9 %) Both: 6 (3.7 %)
Antiepileptic treatment at IRU admission	18 (11.0 %)
Time after event (days)	11.0 [8.0–17.0]
Length of stay (days)	31.0 [25.0–45.5]

Table 2
Presence of seizures, EEG abnormalities.

Number of patients according to seizure timing and ASM presence	**Presence of EEG abnormalitiesat IRU admission**		
	Epileptiform	***Epileptiform & Delta***	***Delta***
With ASM at IRU admission (N = 18)			
5 with ESs			
2 (LSs intra-IRU)	0	0	1
	1	0	0
2 (LSs intra/post-IRU)	0	1	1
(1 No LSs)	0	1	0
13 without ESs			
4 (LSs intra-IRU)	0	0	2
	0	0	0
	0	0	0
9 (No LSs)	0	0	3
	0	0	1
	0	0	0
	0	0	0
	0	0	0
	0	0	0
Without ASM at IRU admission (N = 145)			
6 (LSs intra-IRU)	0	2	1
	0	0	3
2 (LSs post-IRU)	0	0	1
	0	0	1
75 (No LSs)	2	6	67
62 (No LSs)	0	0	0

Abbreviations: ASM: anti-seizure medication; ESs: Early Seizures; IRU: Intensive Rehabilitation Unit; LSs: Late Seizures.

paucity of shared guidelines regarding the management of LSs in post-stroke patients. Consequently, in clinical practice, the selection of the most suitable treatment for each patient was based on a pragmatic approach.

According to the new definition of the ILAE [12], patients already meet the criteria of epilepsy when a single seizure occurs with an enduring cause, for example, stroke. However, questions about the real need to continue treatment (maintaining or changing the ASM) and the risks associated with a possible withdrawal must be addressed during and after rehabilitation.

With only 0.05 % of patients developing post-stroke LSs, we should avoid exposing the majority of patients to unneeded medications. Potential major side effects of ASMs include mood and cognitive alterations, and experimental and clinical studies suggest that some ASMs may inhibit neuroplasticity and stroke recovery [22]. Even though the new generation of ASM is generally more tolerable in stroke survivors [23], still even levetiracetam may cause potentially serious side effects on behaviour (26) that may negatively affect rehabilitation outcomes.

Based on these considerations, we could generally identify three subgroups of patients: (a) patients treated at T0 in the absence of seizures for at least four weeks after admission to the IRU and epileptic discharge on the EEG, most of whom discontinued ASM at T1 and T2; (b) patients receiving ASM during IRU stay because of the presence of ESs and epileptic discharges and (c) patients starting treatment because of LSs occurring during the IRU stay. If on the one hand epilepsy negatively affects activities of daily living, cognitive function, and quality of life [17,18], on the other hand, improper use of ASMs could hamper the functional outcome in post-stroke patients [6]. ASM use may be improper regarding overdosage, inappropriate prescription, when there is no clinical and instrumental evidence of their need, or also inappropriate choice of the most suitable molecule, due to lack of careful evaluation of efficacy, and/or evaluation of side effects and drug-drug interaction. Thus, the evaluation of a proper risk/benefit balance in the use of ASM treatment in a sub-acute stage of post-stroke patients must be considered as one of the aims of the individual rehabilitation project to improve patients' neurological outcomes.

While we found a frequency of 50 % (75/149) of alterations in EEG without clinical manifestation in our cohort, Lasek-Bal et al. [24] found EEG abnormalities in 40 % of patients with acute stroke without epileptic manifestations, showing that these findings were associated with a poor neurological status in the first days and poor functional outcomes in the chronic period of stroke. In hemispheric acute ischemic stroke, several types of EEG changes can be observed: background slowing, arhythmic focal delta activity, and epileptiform discharges [25]. We found all these EEG alterations in our group of patients, with focal slowing being the most frequent, associated with higher LS occurrence.

Bentes et al. found that no EEG abnormality independently predicted acute symptomatic seizures [26,27]. However, EEG slow changes induced by the structural brain lesions probably reflect alterations in the cortical function caused by direct or indirect local neuronal network dysfunction. Although EEG abnormalities of a non-epileptic nature (focal delta slowing) do not have a high predictive power concerning seizure risk, the availability in the rehabilitation facility of an EEG recording can help to define the pathogenesis of acute symptoms such as the appearance of involuntary movements or sudden onset of

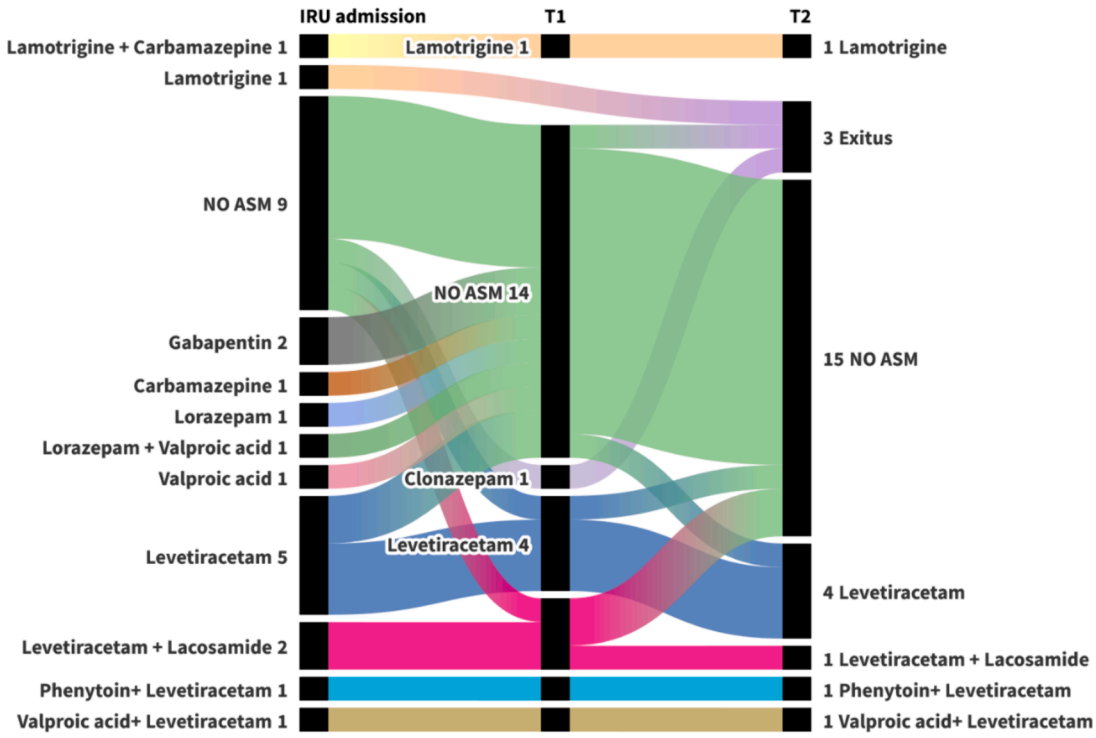

Fig. 2. Alluvial plot of antiepileptic treatment at the three time of evaluation (Intensive Rehabilitation Unit admission, discharge and six months follow-up). All patients with LS are considered.

unexplained behavioral changes or transient loss of consciousness. As reported by many authors [23,26,28] abnormalities on EEG can predict the development of epilepsy in the first year after stroke, independently of clinical and imaging-based infarct severity; ictal and interictal epileptiform discharges, albeit specific, are not so frequent. The most frequent predictive EEG findings are the presence of lateralized periodic discharges, which are more frequently observed in the acute phase [29]. In the post-acute phase, such as in the rehabilitative setting, focal slowing is the EEG finding that is most prevalent in patients with LS, although it should be noted that not all patients with this EEG finding ultimately develop LS [30]. Long-term EEG recordings are of great value [31], but they cannot be obtained in all patients and should be reserved for patients with recurrent behavioural changes [32].

Finally, concerning the use of ASMs, our findings, while reflecting a "real life" management of post-stroke epilepsy in two different Italian regions, are in line with the current literature. Indeed, as stated in a recent review on this field, the regimen of ASM should be based on individual cardiovascular risk, psychosomatic comorbidities, and concomitant medications [33]. Interestingly, despite some patients starting treatment during the IRU stay or in time-frames T1–T2 for the occurrence of LSs, we observed a reduction in the proportion of patients treated with ASM between the time-frames T0 and T2 (from 11 % to 8 %). It is important to highlight that in our sample, most patients discontinuing ASM at discharge without LS after the IRU remained seizure-recurrence-free for the following six months.

As to ASM, we also observed a slight increase in the number of patients in monotherapy and a slight reduction in the number of medications used over time. The current study also revealed a significant prevalence of newer-generation ASM. Indeed, recent RTC suggested that newer-generation ASM could be more effective, compared with older-generation ASM, for treating post-stroke epilepsy in ASM retention and seizure recurrence prevention [23]. Our results showing that levetiracetam was the most frequent drug used at T2 (in six out of nine patients) is in line with these recommendations. However, even levetiracetam, although being probably the most manageable ASM [34], may have detrimental effects on behaviour, especially for those patients suffering from post-stroke depression in whom this ASM treatment may further fuel psychiatric comorbidity [35].

The strength of the current study is that post-stroke patients have been consecutively recruited and well-characterized. However, our cohort is limited to post-stroke patients that did not result in a severe acquired brain injury and our sample was mainly represented by patients with ischemic stroke. The relatively small number of patients with PSE that we could observe is the main limitation of our study. The unavailability of an EEG in some cases is another limitation of our study. Finally, clinical and instrumental data at T2 are not complete, as not all patients were available for follow-up, and this has introduced an attrition and selection bias

Despite these limitations, the results of this study transparently and systematically highlight the current management of treatments and assessment of epileptic seizures in two Italian IRU centres.

5. Conclusions

Our findings underscore the need for greater dissemination of seizure management recommendations in patients with stroke. The rehabilitation pathway is an excellent setting to safely modify the ASM treatment of stroke patients based on clinical evaluations and, when possible, EEG availability, as a part of the individual rehabilitation project.

These observations confirm the importance of research in this field to provide evidence for a constant update of treatment guidelines. Prospective multicentric studies in the post-acute inpatient rehabilitation setting are needed to clarify these aspects and provide evidence for shared recommendations.

Ethics, declarations

- The work described has not been published previously except in the form of a preprint, an abstract, a published lecture, academic thesis or registered report.
- The article is not under consideration for publication elsewhere.

- The article's publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.
- If accepted, the article will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Declarations

Ethical approval: The study was approved by the local ethical committee (CEAVC Em. 2021-007 ID 14513_bio).

Informed consent: Written informed consent was obtained from all subjects before the study.

Trial registration: Name of the registration trial registry: RIPS; Registration number: NCT03866057 (https://clinicaltrials.gov/ct2/show/study/NCT03866057?term=fondazione+don+gnocchi%2C+stroke&draw=2&rank=1).

Guarantor: FC.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author did not use generative AI and AI-assisted technologies.

CRediT authorship contribution statement

Maenia Scarpino: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Antonello Grippo:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **Silvia Campagnini:** Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Bahia Hakiki:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Antonio Maiorelli:** Writing – review & editing, Investigation, Data curation. **Alessandro Sodero:** Writing – review & editing, Investigation, Data curation. **Erika Guolo:** Writing – review & editing, Investigation, Data curation. **Andrea Mannini:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Data curation. **Claudio Macchi:** Writing – review & editing, Supervision, Funding acquisition. **Francesca Cecchi:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data is available upon request to the corresponding author for research purposes.

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