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SHORT COMMUNICATION

Latency of poststroke epilepsy can predict drug resistance

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Abstract

Background and Purpose: The progressive nature of epileptogenesis raises the question of whether the latent period may already carry information about the characteristics of the subsequent epilepsy. This study aimed to explore whether the time from stroke to epilepsy onset was related to the risk of drug resistance in patients with poststroke epilepsy (PSE).

Methods: Patients with epilepsy secondary to cerebral infarct or spontaneous intracerebral hemorrhage were included. Study outcome was the occurrence of drug resistance defined as failure of adequate trials of two tolerated and appropriately chosen and used antiseizure medication schedules to achieve sustained seizure freedom.

Results: One hundred fifty-nine patients with PSE and a median follow-up of 5 (interquartile range [IQR] = 3–9) years were included. In the study cohort, 29 (18.2%) participants were drug resistant. The median length of the time interval between stroke and PSE onset was 13 (IQR = 7–15) months in drug-resistant patients and 19 (IQR = 14–42) months ($p < 0.001$) in patients with seizure control. According to multivariable regression analysis, the time from stroke to PSE was an independent predictor of drug resistance ($p < 0.001$). The risk of drug resistance was highest when the onset of PSE occurred within the first months from stroke and decreased progressively with a steeper decline over the first 12 months.

Conclusions: Substantial variability may exist in the pathways leading to PSE and distinguish patients with a variable risk of drug resistance.

KEYWORDS
brain infarct, cerebral hemorrhage, seizures, stroke

INTRODUCTION

Poststroke epilepsy (PSE) develops in at least 4%–6% of the stroke population and is one of the most common causes of acquired epilepsy [1]. Epileptogenesis is the insult-induced cascade of changes that transform the nonepileptic brain into one that generates spontaneous recurrent seizures. Epileptogenesis is classically thought to involve three stages: (i) the initial precipitating insult, as stroke; (ii) the latent period, which is the interval between the original brain insult and the clinical presentation of the first spontaneous seizure; and (iii) the chronic epilepsy phase [2]. Far from being a stepwise, absolute transition that culminates in the first seizure, epileptogenesis should rather be conceived as a continuum, representing a progressive process that continues into chronic epilepsy with dynamic changes in the neuronal networks [3].

The progressive nature of epileptogenesis raises the question of whether the latent period may carry information about the

characteristics of the subsequent epilepsy, including the resistance to pharmacological treatment. This study aimed to explore whether the time from stroke to epilepsy onset was related to the risk of developing drug resistance in patients with PSE treated with antiseizure medications (ASMs).

MATERIAL AND METHODS

Participants and study outcome

We retrospectively identified patients ≥16 years old who were referred to the Epilepsy Center of the United Hospitals of Ancona and had a diagnosis of epilepsy secondary to cerebral infarct or spontaneous intracerebral hemorrhage and no history of seizures before the stroke [4]. Seizures occurring within and beyond 7 days of stroke onset were classified as acute symptomatic and unprovoked seizures [5]; PSE was diagnosed as the occurrence of one or more unprovoked seizures [5]. The latency of PSE was defined as the time interval (months) between stroke onset and the occurrence of first-time unprovoked poststroke seizure.

Data on demographics, clinical history, medications, and seizure occurrence were collected from medical records. Drug resistance was the study outcome; drug-resistant epilepsy (DRE) was defined as failure of adequate trials of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [6]. Patients with follow-up <12 months were excluded to allow a consistent definition of DRE according to the consensus that seizure-free duration should be at least 12 months [6].

Statistical analysis

Values were presented as mean (SD) or median (interquartile range [IQR]) for continuous variables and as the number (percent) of patients for categorical variables. Comparisons were made through Student *t* test, Mann–Whitney test, or chi-squared test. Due to nonnormal distribution, a logarithmic transformation of the time (months) from stroke to PSE onset was performed. A binary logistic regression adjusted for possible clinical confounders was performed to identify the association between the time from stroke to PSE and drug resistance; any variables with *p*-values <0.05 from comparisons of baseline characteristics were identified for statistical adjustment. The collinearity between exposure variables was assessed with the variance inflation index. Results were reported as odds ratio with associated 95% confidence interval. The potential nonlinear dose–response relationship between the time from stroke to PSE onset and pharmacoresistance was analyzed by restricted cubic spline (RCS) functions with five knots at fixed percentiles of 5%, 27.5%, 50%, 72.5%, and 95%. Results were considered significant for *p*-values <0.05 (two-sided). Data analysis was performed using the Stata/IC 13.1 statistical package (StataCorp).

Standard protocol approvals, registrations, and patient consents

The study was approved by the ethics committee of the Marche Polytechnic University. All participants gave their informed written consent according to the Declaration of Helsinki.

RESULTS

Of 172 patients with PSE initially identified, 13 patients were excluded due to follow-up <12 months. Accordingly, 159 patients with PSE and a median follow-up of 5 (IQR = 3–9) years were included. Twenty-nine (18.3%) participants had DRE. Baseline characteristics of the patients according to drug resistance are summarized in Table 1; see Table S1 for details about the ASMs that patients were taking. Among patients with cerebral infarct, the median latency from stroke to PSE was 6 (IQR = 4–15) months in patients with DRE and 18 (IQR = 13–41) months ($p < 0.001$) in patients with seizure control. Among patients with intracerebral hemorrhage, the median latency was 13 (IQR = 11–15) and 20 (IQR = 16–45) months ($p = 0.004$) in patients with DRE and seizure control, respectively. There were no statistically significant differences in PSE latency by stroke type in cases with DRE ($p = 0.064$) and cases with seizure control ($p = 0.501$).

The time from stroke to PSE onset was an independent predictor of drug resistance ($p < 0.001$), with shorter latency being associated with a higher and longer latency with a reduced risk of DRE (Table 2). The multivariable model did not suffer from collinearity (variance inflation factors: 1.00–1.06). Using RCS multivariable analysis, a linear association between the time from stroke to PSE onset and the risk of drug resistance was found ($p = 0.731$ for nonlinearity). The RCS analysis confirmed the significant association between the PSE latency and the risk of DRE; the risk of DRE was highest when the onset of PSE occurred within the first months after stroke and decreased progressively with a steeper decline over the first 12 months (Figure S1).

DISCUSSION

The novel finding of this study was the relationship between the length of the latent period and seizure control in patients with PSE, a shorter latency from stroke to epilepsy onset being an independent predictor of drug resistance. The association of stroke severity, stroke type, and status epilepticus as the first manifestation of PSE with DRE has already been discussed [4, 7].

The mechanisms underlying epileptogenesis are only partially known, and several pathophysiological hypotheses have been formulated to explain drug resistance. The characteristics of the first stage of epileptogenesis—that is, the initial precipitating insult to the brain—have been explored as possible risk factors for the development of epilepsy and drug resistance. Conversely, the relationship between

TABLE 1 Characteristics of patients with poststroke epilepsy according to drug resistance

Characteristic	Drug responsive, $n = 130$	Drug resistant, $n = 29$	p
Male sex	86 (66.2)	18 (62.1)	0.676
Age at stroke onset, years	57.8 (14.7)	52.1 (15.3)	0.065
Family history of seizures	4 (3.1)	2 (6.9)	0.329
Hypertension	90 (69.2)	18 (62.1)	0.455
Diabetes mellitus	24 (18.5)	6 (20.7)	0.782
Dyslipidemia	51 (39.2)	11 (37.9)	0.897
Atrial fibrillation	19 (14.6)	2 (6.9)	0.267
Coronary heart disease	26 (20.0)	4 (13.8)	0.440
Stroke type			0.016
Cerebral infarct	89 (68.5)	13 (44.8)	
Intracerebral hemorrhage	41 (31.5)	16 (55.2)	
Stroke severity[a]			0.001
Mild to moderate	75 (57.7)	7 (24.1)	
Severe	55 (42.3)	22 (75.9)	
Cortical involvement	87 (68.5)	24 (82.8)	0.126
Early poststroke seizures[b]	16 (12.3)	6 (20.7)	0.237
Epilepsy latency, months[c]	19 [14–42]	13 [7–15]	<0.001
Status epilepticus at epilepsy onset	5 (3.9)	7 (24.1)	<0.001
Seizure types			0.013
Focal onset	67 (51.5)	11 (37.9)	
Focal-to-bilateral tonic–clonic	41 (31.6)	17 (58.6)	
Generalized or unknown onset	22 (16.9)	1 (3.5)	
Follow-up time, years	5 [3–9]	6 [3–12]	0.226

Note: Data are mean (SD) or median [interquartile range] for continuous variables and *n* (%) for categorical variables.

Abbreviation: NIHSS, National Institutes of Health Stroke Scale.

[a]Stroke was defined as mild to moderate if NIHSS score at stroke onset was <16 and severe if initial NIHSS score was ≥16.

[b]Seizures occurring within 7 days of stroke onset.

[c]The latency of epilepsy was defined as the time interval between stroke onset and the occurrence of first-time unprovoked poststroke seizure.

the latent period and epilepsy course has been largely ignored, although it is reasonable to hypothesize that commonalities exist.

The severity and location of the brain injury can play a significant role, as the molecular and cellular changes induced by different types of injuries may differ. Based on observations from animal models of epilepsy, the time needed for focal hippocampal discharges to become clinically obvious events was related to the location and extent of extrahippocampal damage [8]. Prolonged, low-intensity perforant pathway stimulation, which did not cause widespread neuronal damage, was associated with a long latent period [8]. Initially focal, subclinical discharges in minimally damaged brains may face barriers to seizure spread that delay the appearance of clinical seizures [8], and studies with the kindling model indicated that parahippocampal areas function as critical substrates or gates for progression of seizure discharges [9, 10]. Conversely, a more severely damaged seizure circuit may cause even the earliest focal discharges to spread widely and become clinically obvious events without delay [11]. From the perspective of drug resistance, the "intrinsic severity hypothesis" considers drug resistance as an inherent property of epilepsy related to disease severity [12]. Not only a high seizure frequency but also the extent of structural lesions has been mentioned as a measure of epilepsy severity that predicts resistance to treatment [13]. The length of the latent period can be possibly interpreted as a further indicator of intrinsic severity. Furthermore, the "neural network hypothesis" suggests that epilepsy-associated structural alterations contribute to the formation of an abnormal neural network, thereby reducing the efficacy of the ASMs [14], and it appears that the functional alterations in hippocampal pyramidal neurons and dentate gyrus are critically involved in the mechanisms underlying the drug resistance of seizures [12].

Experimental evidence supports the role of brain inflammation in epileptogenesis and epilepsy progression [15]. An inciting epileptogenic brain injury may lead to activation of microglia, astrocytes, and neurons, and dysfunction of the blood–brain barrier in the regions involved in the pathologic event [15]. This chain of consequential or concomitant events results in neuronal hyperexcitability, cell injury, decreased seizure threshold, and network reorganization, which are eventually responsible for seizure generation and recurrence [15]. The evidence that neuroinflammation contributes to pathologic hyperexcitability and disease severity raises the possibility that it may contribute to drug resistance according to the "intrinsic severity" hypothesis. Additional mechanisms may mediate the role of neuroinflammation in DRE; the release of inflammatory mediators by astrocytes and neurons may increase the expression of multidrug efflux transporters in the blood–brain barrier and restrict brain entry of ASMs, the so-called "transporter hypothesis" [12]. There is experimental evidence in support of a link between neuroinflammatory molecules and P-glycoprotein induction [12].

The current study has the merit of developing preliminary insights about the relationship between epilepsy latency and risk of DRE. The main limitation is the retrospective design, which is prone to the risk of bias and misdiagnosis. We could not investigate the role of other potential crucial modifiers of the epileptogenesis and epileptic maturation, like genetic background, epigenetic factors, brain reserve, and poststroke exposure to nongenetic factors. Although no robust evidence exists that ASMs have antiepileptogenic properties, the lack of information about the management of acute symptomatic seizures did not allow exploration of any potential interference of the early administration of ASMs. Prospective studies, larger cohorts of patients, and molecular, neurophysiology, and neuroimaging biomarkers are warranted to validate these findings and provide additional explanations of the underlying pathophysiological mechanisms.

TABLE 2 Association between baseline characteristics and drug resistance

Dependent variable	Adjusted OR (95% CI)[a]	*p*
Epilepsy latency[b]	0.21 (0.09–0.48)	<0.001
Cerebral hemorrhage	5.67 (1.84–17.49)	0.003
Severe stroke	4.10 (1.39–12.12)	0.011
Status epilepticus at epilepsy onset	6.41 (1.36–30.20)	0.019
Type of seizures[c]		
Focal-to-bilateral tonic–clonic	1.71 (0.59–4.95)	0.324
Generalized/unknown onset	0.26 (0.03–2.53)	0.245

Note: Values are from binary logistic regression analysis.

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Adjusted for length of latent period (log transformed), stroke type and severity, status epilepticus at epilepsy onset, and seizure type.

[b]The latency of epilepsy was defined as the time interval (months) between stroke onset and the occurrence of first-time unprovoked poststroke seizure.

[c]Focal onset seizures as reference.

CONCLUSIONS

Epileptogenesis refers to a dynamic process that progressively alters neuronal excitability and results into circuitry reorganization at either the synaptic or the network level. The mechanisms of drug resistance are multifactorial and likely act together or even interact. Substantial qualitative and quantitative variability may exist in the pathways leading to structural epilepsy and may distinguish patients with PSE into different endophenotypes with a variable risk of drug resistance. The early identification of factors predicting treatment response may be of aid to understand the pathophysiology of PSE and hold implications to guide clinicians, counsel patients, and inform the health care system on the required resources when unprovoked seizures occur after a stroke.

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AUTHOR CONTRIBUTIONS

Simona Lattanzi: Conceptualization (lead); formal analysis (equal); methodology (lead); project administration (lead); supervision (equal); writing – original draft (lead); writing – review and editing (lead). **Eugen Trinka:** Writing – review and editing (equal). **Gianni Turcato:** Formal analysis (equal). **Claudia Rinaldi:** Data curation (equal). **Claudia Cagnetti:** Data curation (equal). **Nicoletta Foschi:** Data curation (equal). **Serena Broggi:** Data curation (equal). **Davide Norata:** Data curation (equal). **Francesco Brigo:** Writing – review and editing (equal). **Mauro Silvestrini:** Writing – review and editing (equal).

CONFLICT OF INTEREST

S.L. has received speaker's or consultancy fees from Angelini Pharma, Eisai, GW Pharmaceuticals, and UCB Pharma and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, BIAL, Eisai, and GW Pharmaceuticals. E.T. has received consultancy fees from Arvelle Therapeutics, Argenx, Clexio, Celegene, UCB Pharma, Eisai, Epilog, BIAL, Medtronic, Everpharma, Biogen, Takeda, LivaNova, Newbridge, Sunovion, GW Pharmaceuticals, and Marinus; speaker fees from Arvelle Therapeutics, BIAL, Biogen, Böhringer Ingelheim, Eisai, Everpharma, GSK, GW Pharmaceuticals, Hikma, LivaNova, Newbridge, Novartis, Sanofi, Sandoz, and UCB Pharma; and research funding (directly or to his institution) from GSK, Biogen, Eisai, Novartis, Red Bull, Bayer, and UCB Pharma outside the submitted work. E.T. receives grants from the Austrian Science Fund, the National Bank of Austria, and the European Union. E.T. is the CEO of Neuroconsult. The remaining authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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