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Clinical Profile of Stroke Chameleons Receiving Intravenous Thrombolysis: Insights from a Single-Center Experience

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Keywords
Chameleon · Ischemic stroke · Cerebral infarction · Stroke · Intravenous thrombolysis · Cerebrovascular disease

Abstract
Introduction: In emergency rooms (ERs), 5% of patients experiencing an acute ischemic stroke (AIS) receive an alternative diagnosis; these cases are known as stroke chameleons (SC). The percentage of SC treated with intravenous thrombolysis (IVT) and the characteristics have not been well described. We aimed at investigating the variables associated with the probability receiving IVT. ***Methods:*** In this prospective study, we included consecutive patients with SC admitted at the ER of Clínica Alemana between September 2014 and October 2023. ***Results:*** Among 1,193 stroke patients; sixty-three (5.2%) corresponded to SC. Ten of these cases (15.8%, 95% CI: 8.8–26.8) were treated with IVT, mean door-to-needle (DTN) time of 85.7 (SD 35) min, median of 73.5 (IQR 62–113) min. SCs who underwent IVT were younger (p = 0.01), with higher NIHSS (p = 0.05). They presented more frequently with altered level of consciousness in the NIHSS (p = 0.01), language abnormities (p = 0.001), and dysarthria (p = 0.01). In multivariate analysis, none of the variables were significantly associated with IVT. A secondary analysis showed that only time to brain imaging was significantly associated with IVT (OR: 0.99; 95% CI: 0.98–0.99; p = 0.01). ***Conclusions:*** Almost 1 out of every 7 SC could be treated with IVT but with a prolonged DTN time; the chance of being treated is associated with time to brain imaging.

Introduction

In emergency rooms (ERs), 5%–15% of patients experiencing an acute ischemic stroke (AIS) end up receiving an alternative diagnosis; these cases are known as stroke chameleons (SCs) and may not receive appropriate

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acute medical care [1, 2]. The percentage of SC treated with intravenous thrombolysis (IVT) and the characteristics have not been well described. We aimed at investigating the variables associated with the probability receiving IVT.

Methods

In this prospective study, we included consecutive patients with SC admitted at the emergency department (ED) of Clínica Alemana de Santiago between September 2014 and October 2023. SCs were defined as patients who consulted at the ER with symptoms of stroke that were missed by the triage nurse and an internist physician who is usually the first doctor that sees the patient, and from whom a neurological evaluation was requested to rule out a diagnosis different from stroke, or a patient with an acute syndrome leading to admission, with an initial admitting diagnosis different from stroke, but in whom it is later determined that their admission symptoms were caused an AIS.

We collected data including pre-stroke modified Rankin Scale score (mRS), sex, age, cardiovascular risk factors, time from symptom onset (defined as the last time the patient was known to be neurologically deficit free) to ER arrival, and blood pressure from patient records. Subsequently, patients were subjected to a comprehensive neuroimaging protocol as previously described [3].

Patients eligible for IVT were treated within a 4.5-h time window. Since 2018, patients experiencing a wake-up stroke or an unknown symptom onset undergo additional imaging with FLAIR or CT perfusion and may be treated with IVT if the imaging indicates a favorable profile. The specific imaging protocol for these patients was determined by the attending neurologist [4, 5].

The NIHSS on admission was reconstructed from clinical notes [6] by one of the investigators (A.M.B.). The Ethics Committee of Clínica Alemana de Santiago, Universidad del Desarrollo, granted approval for the registry, written informed consent was obtained from all participants, and for vulnerable participants, consent was provided by a parent, legal guardian, or next of kin.

Statistical Analysis

Statistical analysis was conducted using SPSS software (version 14; SPSS, Inc, Chicago, IL, USA). We determined the proportion of SC, who received IVT. Univariate analysis with Fisher's exact test of independence was performed to evaluate the associations of treatment with IVT and basal mRS, sex, age, cardiovascular risk factors, previous use of anticoagulants, time from symptom onset to ED, admission NIHSS, the different components of NIHSS, dichotomized as present or absent, systolic blood pressure and diastolic blood pressure at admission, time to brain imaging, stroke location in the anterior, posterior, or both arterial circulations, presence of large vessel occlusion, and etiological classification according to TOAST at discharge. A logistic regression analysis was performed for those variables that were associated ($p < 0.25$, Hosmer Lemeshow criteria for fishing variables) in the univariate analysis, to select the final multivariate model.

Results

Among 1,193 stroke patients, sixty-three (5.2%, 95% CI: 4.1–6.6) corresponded to SC. Ten of these cases (15.8%, 95% CI: 8.8–26.8) were treated with IVT, with a mean door-to-needle (DTN) time of 85.7 (SD 35) min and a median of 73.5 (IQR 62–113) min. Only 1 patient (1.5%) was treated with a DTN time of less than 60 min. The baseline characteristics of SC patients are shown in Table 1. SCs who underwent IVT were younger ($p = 0.01$), with higher NIHSS ($p = 0.05$), compared to non-thrombolysed SC. They presented more frequently with altered level of consciousness in the NIHSS ($p = 0.01$). They also had more frequently facial weakness ($p = 0.063$), language abnormities ($p = 0.001$) and dysarthria ($p = 0.01$). They were less likely to have high blood pressure ($p = 0.084$) and had a lower use of anticoagulant therapy ($p = 0.187$). In multivariate analysis, none of the variables included in the model were significantly associated with IVT. A secondary analysis was performed, based on the small number of SC patients taking into account only those elements that a stroke neurologist (A.M.B.) and an expert in medical statistics (G.C.) considered could be the most relevant: patient's age, presence of high blood pressure, previous use of oral anticoagulation, time to the ED and time to brain imaging, initial NIHSS score, and the presence of large vessel occlusion. This analysis showed that only time to brain imaging was significantly associated with IVT (OR: 0.99; 95% CI: 0.98–0.99; $p = 0.01$). The diagnoses received in the ER by SC included metabolic encephalopathy (17.4%), migraine (14.2%), seizures (11.1%), and psychiatric disorders (6.3%) as the most frequent alternative diagnoses.

Table 1. Univariate analysis of clinical and radiological variables of SC patients according to thrombolysis treatment at the ER

Variables	Total SC group (*N* = 63)	SC not treated with IVT (*N* = 53)	SC treated with IVT (*N* = 10)	*p* value
Age, years				
Mean±SD	59±21.3	62.7±20	46.2±18	0.01
Median (IQR)	55 (41–78)	67 (41–78)	41 (61–84)	
Female sex, *n* (%)	33 (52.3)	28 (52.1)	5 (50)	1
Previous disability				
Rankin >3, *n* (%)	9 (14.2)	7 (13.2)	2 (20)	0.62
Rankin median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	
Hypertension, *n* (%)	36 (57.1)	33 (62.2)	3 (30)	0.084
Diabetes mellitus, *n* (%)	19 (30.1)	16 (30.1)	3 (30)	1
Hypercholesterolemia, *n* (%)	22 (34.9)	18 (33.9)	4 (40)	0.72
Tobacco, *n* (%)	12 (19)	11 (20.7)	1 (10)	0.67
Atrial fibrillation, *n* (%)	11 (17.4)	10 (18.8)	1 (10)	0.676
Coronary disease, *n* (%)	10 (15.8)	10 (18.8)	0 (0)	0.34
Previous use of anticoagulation, *n* (%)	11 (17.4)	11 (20.7%)	0 (0)	0.187
Time to ER[a], min				0.12
Mean±SD	1,021.5±2,023.9	1,097.2±2,065	70±68	
Median (IQR)	240 (90–1,120)	314 (120–1,200)	62 (18–76)	
NIHSS at admission				0.05
Mean±SD	3.2	2±3.1	8.4±9.7	
Median (IQR)	1 (1–3)	1 (0–2)	3.5 (2–11)	
NIHSS components, presence of sign, *n* (%)				
1a. Level of consciousness	6 (9.5)	4 (7.5)	2 (20)	0.24
1b. Level of consciousness questions	20 (31.7)	14 (26.4)	6 (60)	0.061
1c. Level of consciousness commands	8 (12.6)	4 (7.5)	4 (40)	0.017
2. Best gaze	2 (3.1)	1 (1.89)	1 (10)	0.294
3. Visual	9 (14.2)	6 (11.3)	3 (30)	0.145
4. Facial weakness	11 (17.4)	7 (13.2)	4 (40)	0.063
5. Motor arm				
Left arm	3 (4.7)	2 (3.7)	1 (10)	0.41
Right arm	10 (15.8)	8 (15)	2 (20)	0.653
6. Motor leg				
Left leg	3 (4.7)	2 (3.7)	1 (10)	0.4
Right leg	6 (9.5)	4 (7.5)	2 (20)	0.24
7. Limb ataxia	5 (7.9)	4 (7.5)	1 (10)	1
8. Sensory abnormalities	7 (11.1)	6 (11.3)	1 (10)	1
9. Best language	15 (23.8)	8 (15)	7 (70)	0.001
10. Dysarthria	8 (12.6)	4 (7.5)	4 (40)	0.017
11. Extinction and inattention	0	0	0	
Systolic BP, mean±SD, mm Hg	139.1±29	138.8±28.5	139±35.5	0.93
Diastolic BP, mean±SD, mm Hg	77.9±15.7	77.5±14.8	87.3±20.6	0.09
Stroke location, *n* (%)				
Supratentorial	37 (58.8)	29 (54.7)	8 (80)	0.005
Infratentorial	14 (22.2)	13 (24.5)	1 (10)	
Both	12 (19)	11 (20)	0.1 (10)	

Table 1 (continued)

Variables	Total SC group (N = 63)	SC not treated with IVT (N = 53)	SC treated with IVT (N = 10)	p value
Circulation affected, *n* (%)				
Anterior	30 (47.6)	23 (43.3)	7 (70)	0.32
Posterior	29 (46)	26 (49.2)	3 (30)	
Both	4 (6.3)	4 (7.5)	0 (0)	
Time to brain imaging, min				0.05
Mean±SD	1,560±2,205	2,304±2,304	149.6±90.2	
Median (IQR)	756 (180–2,000)	1,344 (465–2,800)	121 (90–160)	
Arterial occlusion on CTA[b], *n* (%)	17 (26.9)	12 (23.5)	5 (50)	0.124
IVT, *n* (%)	10 (15.8)	0	10 (100)	
TOAST etiology, *n*				0.078
Atherosclerotic	7	7	0	
Cardioembolic	17	16	1	
Undetermined	23	15	8	
Lacunar	4	4	0	
Other	12	11	1	

[a]Time from symptom onset to arrival at the emergency room. [b]Spiral computed tomographic angiography of the cervical and intracranial arteries.

Discussion

We found that approximately 15% of SC patients admitted to the ED were treated with IVT. To our knowledge, this number has not been previously reported. This percentage is lower than that of patients initially diagnosed as AIS at our center, which is 30%. Additionally, SC patients had a DTN time nearly double that of our AIS patients, with a mean DTN time of 85.7 min (SD 35), a median of 73.5 min (range 62–113), compared to a mean of 43.6 min (SD 23.8) and a median of 38 min (range 25–48) for AIS patients [7, 8].

When we analyzed those variables that were associated with the chance of a SC patient being treated with IVT, only the time to brain imaging remained significant. This probably reflects the fact that the request of brain imaging is indicating that there is a reasonable suspicion that the patient may be suffering from AIS, and it is a key element for IVT [9]. Indeed, for every minute brain imaging is delayed, the chances of being treated with IVT decreases by 1%; this reflects the importance of reacting rapidly once cerebral ischemia is suspected. SCs were given various admission diagnoses, including toxic-metabolic encephalopathies, migraines, and seizures, consistent with the findings of another study [10].

This study has several limitations. First, this is a single-center study that included a reduced number of patients; additionally, in our center, patients with alterations of mental status, sensory complaints, or non-focal weakness are frequently evaluated in the ED by a neurologist and with DWI-MRI; this could lead to diagnose AIS in patients whose symptoms raise a low level of suspicion. The NIHSS score of SC was reconstructed in a valid retrospective way, and is quite impossible to know exactly how frequent chameleons are, because we know only those SCs that were finally identified as strokes.

In conclusion, almost 1 out of every 7 SC could be treated with IVT but with a prolonged DTN time; the chance of being treated is associated with time to brain imaging and thus early suspicion.

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Statement of Ethics

The Ethics Committee of Clínica Alemana de Santiago, Universidad del Desarrollo, granted approval for the registry (number 2010-11), written informed consent was obtained from all participants, and for vulnerable participants, consent was provided by a parent, legal guardian, or next of kin.

Conflict of Interest Statement

Alejandro M. Brunser reports research grant from Clínica Alemana de Santiago, Unidad de Neurología Vascular, Servicio de Neurología, Departamento de Neurología y Psiquiatría, Clínica Alemana de Santiago, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, and from CONICYT Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) Regular 1181238 during the conduct of the study. Pablo M. Lavados reports research grants from Boehringer-Ingelheim, Bristol Meyer Squibb, and Clínica Alemana de Santiago during the conduct of the study; personal fees from Pfizer; and a research grant from Agencia Nacional de Investigación y Desarrollo Fondecyt 1181333 outside the submitted work. Paula Muñoz reports research grant from Clínica Alemana de Santiago and from CONICYT Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) Regular 1181238 during the conduct of the study. Verónica Olavarria reports receiving research grant from Clínica Alemana de Santiago and Boehringer-Ingelheim for the RECCA study and a research grant from Agencia Nacional de Investigación y Desarrollo Fondecyt 1181333 outside the submitted work. Eloy Mansilla, Maria Elena Trejo, and Pablo González Valdivieso report no conflicts of interest.

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Author Contributions

A.M.B., P.M.L., P.M.-V., E.M., G.C., and V.V.O. contributed to the design and interpretation of the data and drafted the manuscript; A.M.B., M.E.T., and P.E.G. contributed to the data collection of the study; P.E.G., A.M.B., G.C., P.M.L., E.M., M.E.T., and P.M.-V. performed the statistical analysis; P.M.L., G.C., A.M.B., P.E.G., and V.V.O. contributed to interpreting results and reviewing the manuscript and approved the final version of the manuscript; and V.V.O. has primary responsibility for final content.

Data Availability Statement

The data supporting the findings of this study are not publicly available due to the presence of information that could compromise the privacy of research participants. However, the data are available from A.M.B. (abrunser2017@gmail.com) upon reasonable request.

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