ORIGINAL ARTICLE

Clinical features and predictors of delayed neurological syndrome in carbon monoxide poisoning: the AMICO study

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Objectives. To identify predictors for developing delayed neurological syndrome (DNS) after an initial episode of carbon monoxide (CO) poisoning in the interest of detecting patients most likely to develop DNS so that they can be followed.

Methods. Retrospective review of cases of CO poisoning treated in the past 10 years in the emergency departments of 4 hospitals in the AMICO study (Spanish acronym for the multicenter analysis of CO poisoning). We analyzed demographic characteristics of the patients and the clinical characteristics of the initial episode. The records of the cohort of patients with available follow-up information were reviewed to find cases of DNS. Data were analyzed by multivariant analysis to determine the relationship to characteristics of the initial exposure to CO.

Results. A total of 240 cases were identified. The median (interquartile range) age of the patients was 36.2 years (17.6-49.6 years); 108 patients (45.0%) were men, and the poisoning was accidental in 223 cases (92.9%). The median carboxyhemoglobin concentration on presentation was 12.7% (6.2%-18.7%). Follow-up details were available for 44 patients (18.3%). Eleven of those patients (25%) developed DNS. A low initial Glasgow Coma Scale score predicted the development of DNS with an odds ratio (OR) of 0.61 (95% CI, 0.41-0.92) and an area under the receiver operating characteristic curve of 0.876 (95% CI, 0.761-0.990) (P <.001).

Conclusions. The initial Glasgow Coma Scale score seems to be a clinical predictor of DNS after CO poisoning. We consider it important to establish follow-up protocols for patients with CO poisoning treated in hospital EDs.

Keywords: Carbon monoxide poisoning. Neurotoxicity. Delayed neurological syndrome. Carboxyhemoglobin. Glasgow Coma Scale. Prognosis.

Caracterización clínica y factores predictivos de desarrollo de síndrome neurológico tardío en la intoxicación por monóxido de carbono: estudio AMICO

Objetivos. Identificar factores pronósticos de desarrollo de síndrome neurológico tardío (SNT) después de un episodio inicial de intoxicación por monóxido de carbono (ICO), con el fin detectar precozmente a la población más susceptible y facilitar su acceso a un seguimiento específico.

Métodos. Revisión retrospectiva de todos los casos de ICO que acudieron a los servicios de urgencias (SU) de 4 hospitales durante los últimos 10 años. Se analizaron datos demográficos y características clínicas en el momento del episodio. En la cohorte de pacientes con datos de seguimiento disponibles, se evaluó la aparición de SNT y su relación con diferentes variables en la exposición inicial al CO a través de técnicas de análisis multivariante.

Resultados. Se identificaron 240 pacientes. La mediana de edad fue de 36,2 años (17,6-49,6). De ellos 108 (45,0%) eran hombres y 223 casos (92,9%) fueron accidentales. El nivel medio de COHb fue del 12,7% (6,2-18,7). En 44 (18,3%) episodios se disponía de datos de un seguimiento específico. En esta cohorte, 11 (25%) pacientes desarrollaron SNT. Una puntuación inicial más baja en la Escala Coma de Glasgow (GCS) (OR: 0,61, IC 95%: 0,41-0,92) fue predictor independiente del desarrollo del SNT, con un ABC en la curva COR de 0,876 (IC 95%: 0,761-0,990, p < 0,001).

Conclusiones. Una puntuación inicial baja en la GCS parece ser un predictor clínico de desarrollo de SNT en la ICO. Dada la incidencia de SNT, consideramos fundamental establecer protocolos de seguimiento específico de estos pacientes tras su asistencia inicial en los SU.

Palabras clave: Intoxicación por monóxido de carbono. Neurotoxicidad. Síndrome neurológico tardío. Carboxihemoglobina. Escala Coma de Glasgow. Pronóstico.

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Introduction

Carbon monoxide intoxication (COI) is one of the leading causes of mortality and morbidity attributable to poisoning worldwide,[1] with an incidence and mortality rate of 137 and 4.6 cases per million inhabitants each year.[2] Currently its incidence has increased, probably due to the energy crisis and the rising cost of electricity and gas.[3] In Spain, the most frequent cause of COI is poor combustion of boilers for heating or hot water, although it can also occur in the context of fires or even in more recreational settings (use of sishas or hookahs).[4]

Regardless of the source and reason for poisoning (accidental or suicidal), from a pathophysiological point of view carbon monoxide (CO) binds to hemoglobin with much higher affinity than oxygen, forming carboxyhemoglobin resulting in severe tissue hypoxia, primarily affecting the central nervous system and myocardium, as well as the generation of free radicals.[5] Impaired mitochondrial oxidative phosphorylation has been extensively documented in the heart, where mitochondrial dysfunction due to CO can lead to reversible, self-limiting myocardial dysfunction despite adequate oxygen supply.[6]

CO is an imperceptible gas whose intoxication causes very nonspecific symptoms, which makes it a commonly underdiagnosed disease.[7] The range of symptoms it can cause is wide, from mild symptoms (headache, dizziness, asthenia, nausea) to more severe ones (syncope, arrhythmias, chest pain, convulsions, coma) and even death.[8]

According to previous studies, 15-40% of patients exposed to CO may develop delayed neuropsychiatric symptoms leading to delayed neurological syndrome (DNS). This appears 3 to 40 days after initial exposure, and manifests itself in a plural and variable manner in the form of apathy, memory impairment, disorientation, mutism, irritability, inability to concentrate, personality changes, emotional lability, neuropathy, incontinence, chorea, apraxia, psychosis, dementia and parkinsonism.[9-11] At present, the criteria for diagnostic confirmation and the mechanisms that cause DNS are still not well defined, although some authors have recently linked its occurrence to low Glasgow Coma Scale (GCS) scores in the acute phase of intoxication.[12] The detection of damage in the white matter and hippocampus or demyelination phenomena in MRI scans of patients with DNS would support this theory.[12-15] Other proposed theories relate its development to some predisposing factors: advanced age, duration of exposure, delay in the start of treatment, oxidative stress with increased lactate concentrations or presence of hyperthermia, but there is no clear consensus.[12,16-18]

Given the significant number of patients with COI who develop DNS, it seems a priority to dedicate efforts to the early detection of patients susceptible to DNS. Therefore, the aim of this study is to identify these prognostic factors for the development of DNS after the initial episode of COI, to facilitate access to specific follow-up after emergency department (ED) care.

Methods

Study design

Multicenter observational study carried out in the ED and clinical toxicology units of 4 tertiary level hospitals in different regions of Spain. In three of them, after care in the ED, follow-up was carried out in a clinical toxicology outpatient clinic. The patients included in the study were retrospectively selected from the patient registry of the ED or clinical toxicology units of the participating hospitals. All information was collected from the patient's medical record in an anonymized database.

The study was approved by the Research Ethics Committee (CEIm) of the Hospital Universitario Puerta de Hierro Majadahonda (PI 167/21) and was conducted in accordance with the Declaration of Helsinki and the Standards of Good Clinical Practice. The CEIm waived the need to request informed consent.

Study population

All patients presenting to the ED between 2012 and 2021 with a diagnosis of COI, diagnosed as the presence of appropriate symptoms, history suggestive of exposure, and elevated carboxyhemoglobin concentrations, were included. Only cases of pure CO intoxication were included. Those poisoned by fire smoke were excluded, as it was considered that other toxicants such as cyanide were involved during the poisoning episode.[19]

Variables

Baseline and follow-up data (up to 1 year after the initial episode) of the included patients were collected through the clinical history, as well as demographic data and previous medical history. In addition, information was collected on the timing, cause, and source of the COI. At the time of patient inclusion in the study, clinical and analytical aspects related to intoxication were collected: symptoms, physical examination, analytical parameters, outcome and duration of hospitalization and ED stay.

We also collected data related to the incidence of DNS, imaging tests and subsequent follow-up if available (mainly magnetic resonance imaging –MRI–).

The primary endpoint was the development of DNS. DNS was defined as any new neuropsychiatric finding or symptom (including cognitive impairment, dysarthria, dyspraxia, dyspraxia, motor deficits, parkinsonism, memory impairment, seizures, psychosis, and mood disorders) recorded by the clinician when following up patients independently of the study.[20]

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 25.0 (SPSS Inc., Chicago, IL, USA).

Continuous variables were expressed as mean and standard deviation or median and interquartile range (25th and 75th percentiles). Categorical variables were presented as frequencies. The Student t test or Mann-Whitney U test was used for the comparison of continuous variables, according to the normality of the distribution, which was tested using the Kolmogorov-Smirnov test. The chi-square test or Fisher's exact test was used to compare categorical variables.

To determine the independent predictors of DNS, variables were first examined by univariate logistic regression analysis and those with a *P* value < .20 were subsequently analyzed by multivariate logistic regression using the backward stepwise elimination method. Odds ratios and 95% confidence intervals (CI) were also calculated for the variables included in the regression model. The receiver operating characteristic (ROC) curve was used to determine the accuracy of the regression model in predicting the development of DNS. The area under the curve (AUC) and a 95% confidence interval (CI) were calculated for the model's prediction of DNS. A bilateral *P* value < .05 was considered statistically significant.

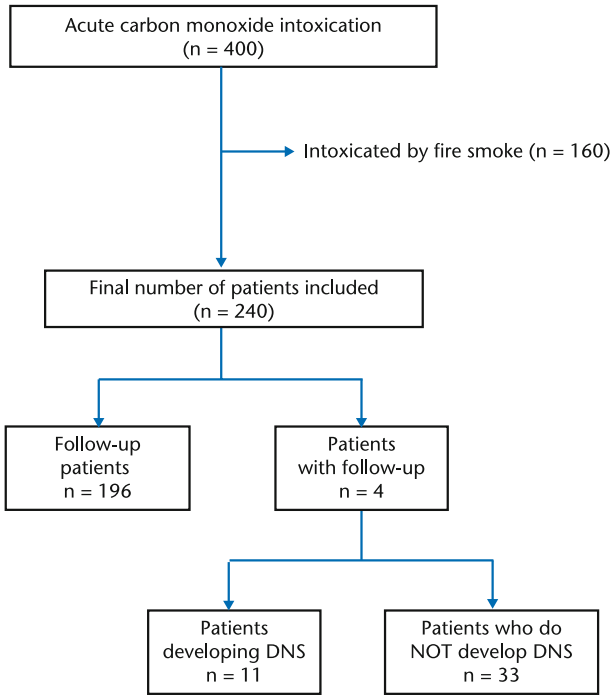

Figure 1. Flow chart of patient selection.
LNS: late neurological syndrome.

Results

During the study period, 400 cases of COI were identified. One hundred and sixty cases occurred in the context of fire smoke inhalation were excluded. Finally, 240 patients were included in the study (Figure 1). The median age was 36.2 years (IQR 17.6-49.6), where 108 (45.0%) were male and 223 cases (92.9%) were accidental. Most poisonings occurred in the home (n = 200, 83.3%), and the main source of CO was incomplete combustion of boilers (n = 62, 25.8%), followed by braziers (n = 54, 22.5%) and heaters (n = 33, 13.8%). The duration of CO exposure averaged 4.3 hours (IQR 2.0-6.0) (Table 1).

At presentation, the median carboxyhemoglobin of the patients was 12.7% (6.2-18.7). The most prevalent intoxication symptoms were headache (n = 136, 56.7%), dizziness (n = 129, 53.8%) and weakness (n = 80, 33.3%). The median baseline GCS score was 15 (15-15). Eleven patients (4.6%) required admission to hospital beds, 8 of them to the intensive care unit (ICU), and none died (Table 1).

Forty-four patients (18.3%) had follow-up data available in the medical record. In this cohort, 11 patients (25.0%) developed DNS. The most common presenting symptoms were disorientation (7, 63.6%), confusion (5,45.5%), worsening recent memory (4, 36.4%), depression and asthenia (Table 2).

MRI was performed on 16 of the 44 patients in the cohort with follow-up. Of these, 10 (62.5%) showed acute brain lesions (ABL). In 8 of these patients with ABI (80%) there were symptoms or signs of DNS, the other 2 patients with alterations in the MRI did not present any symptoms compatible with DNS.

In the univariate analysis, the following factors were associated with the development of DNS: initial GCS score, initial laboratory tests (creatine kinase) and presence of confusion at the time of intoxication (Table 3). Patients with GCS score < 14 had a significantly higher risk of developing DNS (58.3% vs. 12.5%; P .004). Multivariate analysis revealed that, of these possible risk factors, only an initial GCS score < 14 (OR: 0.61, 95% CI: 0.41-0.92) was an independent predictor of the development of DNS (Figure 2). In the ROC curve constructed to determine the accuracy of the regression model in predicting the development of DNS, the AUC value was 0.876 (95% CI: 0.761-0.990, *P* < .001) (Figure 3).

Discussion

In the present study, carried out in four hospitals in different autonomous communities, which are also reference centers in their respective territories and have multidisciplinary clinical toxicology units or teams that follow up cases of poisoning, it has been possible to establish for the first time the percentage of incidence of DNS in patients who suffered an COI in Spain unrelated to smoke inhalation. This has been quantified in 25% of the patients who were followed up. These results agree with previous research and warn of the potential risk of this disease.[21-23]

This incidence reaffirms the great importance of carrying out a specific follow-up of patients who are discharged from the ED after receiving initial care for an COI, as this is not currently done systematically. In Spain, where the specialties of Emergency Medicine

Table 1. Demographic, epidemiological and clinical characteristics of the patients included in the study

	Total N = 240 n (%)
Age (years) [median (IQR)]	36.2 (17.6-49.6)
Sex: Man	108 (45.0)
Comorbidities	
Cognitive impairment	2 (0.8)
Chronic cerebrovascular disease	2 (0.8)
Epilepsy	4 (1.7)
Chronic headache	4 (1.7)
Other NS problems	2 (0.8)
Ischemic heart disease	6 (2.5)
Arrhythmias	2 (0.8)
Other cardiovascular problems	17 (7.1)
Cause of Intoxication	
Accidental	223 (92.9)
Suicide	8 (3.3)
Other	5 (2.1)
NA	4 (1.7)
CO Source	
Boiler	62 (25.8)
Brazier	54 (22.5)
Stove	33 (13.8)
Generating compressor	31 (12.9)
Vehicle	12 (5.0)
Others	13 (5.4)
NA	35 (14.6)
Exposure time (hours) (N = 51) [median (IQR)]	4.3 (2.0-6.0)
Initial symptomatology	
Headache	136 (56.7)
Dizziness	129 (53.8)
Weakness/asthenia	80 (33.3)
Nausea or vomiting	65 (27.1)
Syncope	71 (29.6)
Confusion	38 (15.8)
Dyspnea	22 (9.2)
Palpitations	11 (4.6)
Ataxia	9 (3.8)
Seizures	8 (3.3)
Cough	8 (3.3)
Chest pain	5 (2.1)
Initial vital signs	
Heart rate (bpm) [median (IQR)]	87 (76-100)
Systolic blood pressure (mmHg) [median (IQR)]	1223 (112-136)
Diastolic blood pressure (mmHg) [median (IQR)]	72.5 (62-85)
Body temperature (°C) [median (IQR)]	36.1 (35.8-36.7)
Respiratory rate (rpm) [median (IQR)]	16 (14-22)
GCS alterations	8 (3.3)
GCS score at presentation [median (IQR)]	15 (15-15)
GCS score at presentation [mean (SD)]	14.2 (2.5)
Initial laboratory findings [median (IQR)]	
Leukocytes (x 10^3/mm^3)	9.3 (7.4-11.5)
Lactate (mmol/L)	2.0 (1.06-10.0)
Creatine kinase (U/L)	129.0 (87.2-182.7)
Arterial pH	7.40 (7.37-7.45)
Carboxyhemoglobin (%)	12.7 (6.2-18.7)
Time between end of exposure and 1st carboxyhemoglobin (N = 62), hours, [median (IQR)]	4.0 (2.0-6.0)
Hyperbaric chamber treatment	47 (19.6)
Time to emergency room admission (hours) [median (IQR)]	6.0 (4.0-9.0)

IQR: interquartile range; CO: carbon monoxide; NA: not available; NS: nervous system; SD: standard deviation.

Table 2. Neurological signs and symptoms in patients who developed late neurological syndrome

	Total N = 11 n (%)
Disorientation	7 (63.6)
Confusion	5 (45.5)
Memory impairment	4 (36.4)
Depression/sadness	4 (36.4)
Asthenia	4 (36.4)
Difficulty concentrating	3 (27.3)
Apraxia	2 (18.2)
Irritability	1 (9.1)
Headache	1 (9.1)
Drowsiness	1 (9.1)
Gait disturbance	1 (9.1)
Agnosia	1 (9.1)
Motor aphasia	1 (9.1)
Amnesia	1 (9.1)
Insomnia	1 (9.1)
Paraparesis	1 (9.1)

and Clinical Toxicology are still not officially recognized, the follow-up of these patients after emergency care is uneven and lacks a standardized planning.[24]

The reasons for this lack of specific follow-up (less than 20% in the series, carried out in hospitals with a sensitized approach to these diseases), even when it is offered, may be due to the absence of symptoms on the part of the patient, who dismisses the need to attend check-ups, or denotes a lack of awareness (or time) in the professionals to explain the importance of carrying out such follow-up after discharge of the patient.

The results of this study coincide with those of Namgung et al. The present series confirms that the initial neurological situation (low GCS score) is a predictive factor for the development of DNS.[12,22]

Despite the unspecificity of the GCS in the assessment of coma in intoxicated patients, the diffusion and universal use of the GCS in EDs around the world since the 1980s has led to its score being incorporated into the routine care of any critical patient, including patients with non-traumatic diseases for which it was initially designed in 1974.[25] Therefore, we consider it crucial to detect and adequately record the GCS score early, as an alarm tool to select the most appropriate patients for continuity of care.

From a theoretical point of view, it would be expected that these neurological symptoms would be correlated with higher carboxyhemoglobin levels, but this issue is not without controversy. Some authors have proposed that a correlation between high carboxyhemoglobin concentration and the development of DNS should not always be expected,[26-28] while others claim the opposite.[29] However, it is important to keep in mind that carboxyhemoglobin measurement is difficult to compare between patients, due to variations in the methods of determination (nail bed pulse oximetry or blood cooximetry) and the timing of measurement (at the incident site[30] or on arrival at the ED).[31] In this

Table 3. Predictors of late neurological syndrome determined by univariate and multivariate logistic regression analysis

	Univariate analysis		Multivariate analysis	
	OR 95%CI	*P*	OR 95%CI	*P*
Age (years)	1.02 (0.97-1.06)	.425	Not included	
Sex: Man (%)	1.14 (0.27-4.76)	.854	Not included	
Comorbidities				
Ischemic heart disease	1.55 (0.12-18.96)	.730	Not included	
Exposure time (hours)	1.41 (0.57-3.44)	.456	Not included	
Initial symptomatology				
Headache	0.76 (0.18-3.19)	.709	Not included	
Dizziness	0.66 (0.15-2.79)	.567	Not included	
Weakness/asthenia	1.29 (0.31-5.27)	.723	Not included	
Nausea or vomiting	2.76 (0.68-11.19)	.148	3.57 (0.44-29.15)	.235
Confusion	4.46 (1.05-19.02)	**.036**	5.78 (0.78-20.08)	.145
Seizures	3.20 (0.18-55.95)	.403	Not included	
Syncope	3.19 (0.72-14.25)	.117	1.60 (0.24-10.57)	.627
Palpitations	0.72 (0.07-7.27	.784	Not included	
Initial vital signs				
Heart rate (bpm)	0.98 (0.94-1.02)	.336	Not included	
Systolic blood pressure (mmHg)	0.99 (0.94-1.04)	.696	Not included	
Diastolic blood pressure (mmHg)	0.98 (0.92-1.03)	.728	Not included	
Body temperature (°C)	0.65 (0.17-2.53)	.536	Not included	
Respiratory rate (rpm)	0.93 (0.85-1.13)	.898	Not included	
GCS score at presentation	0.58 (0.38-0.87)	**.009**	0.61 (0.41-0.92)	**.017**
Initial laboratory findings				
Leukocytes (x 10^3/mm^3)	1.06 (0.85-1.32)	.610	Not included	
Lactate (mmol/L)	1.01 (0.93-1.07)	.977	Not included	
Creatine kinase (U/L)	1.00 (1.00–1.01)	**.003**	1.03 (0.96–1.27)	.084
Arterial pH	0.01 (0.00-18.25)	.220	Not included	
Carboxyhemoglobin (%)	1.03 (0.95-1.11)	.459	Not included	
Emergency room admission time (hours)	0.99 (0.96-1.03)	.699	Not included	
Hyperbaric chamber treatment	2.10 (0.57-8.37)	.288	Not included	

OR: odds ratio; CI: confidence interval; GCS: Glasgow Coma Scale.
Values in bold denote statistical significance ($P < .05$).

regard, this series provides experience in which, despite the biases mentioned above, no significant differences in mean carboxyhemoglobin levels were found between patients with DNS and those without.

Furthermore, no significant differences were found in lactate concentration[18,32] or leukocyte count[22] between patients who developed DNS and those who did not, although it has been proposed that they could be predictive markers of its development, although no study included long-term follow-up of patients.

Importantly, numerous studies have been conducted

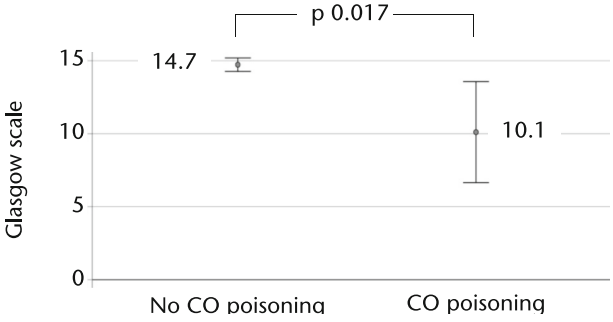

Figure 2. Glasgow Coma Scale score and development of late neurological syndrome.
DNS: late neurological syndrome.

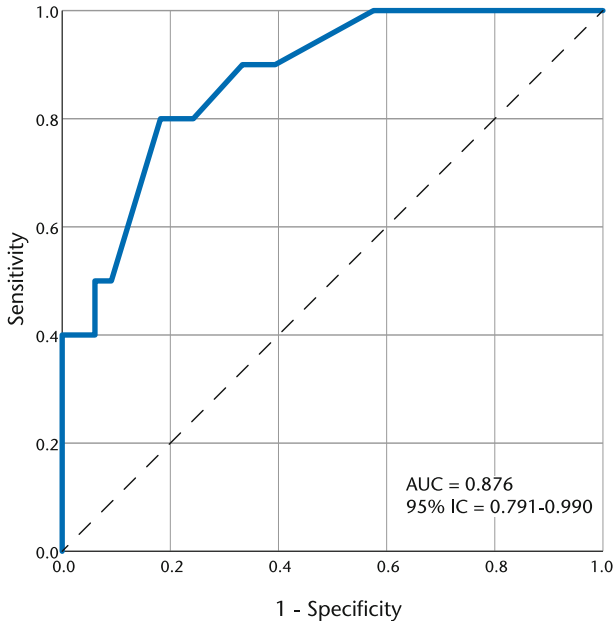

Figure 3. Multivariate logistic regression receiver operating characteristic (ROC) curve for predicting late neurological syndrome.
AUC: area under the curve; CI: confidence interval.

with the aim of identifying specific biomarkers that can predict the development of DNS.[28-32] However, to date, these biomarkers are neither available nor accessible in the ED. Therefore, we believe that GCS score estimation may be a useful tool to assess the risk of developing DNS and should be considered in decision making because of its ease of management and wide acceptance in the ED.

Regarding MRI, performed between 30 and 100 days after COI, 62.5% of the patients in this cohort who underwent MRI showed acute brain lesions. Most of these (80%) had symptoms of DNS, but in 20% of the cases we observed alterations in the MRI without symptoms compatible with DNS. These asymptomatic patients, but with alterations in neuroimaging tests, should be alarming for two reasons. On the one hand, they should raise the possibility of symptoms appearing at much later stages than those defined to date, which should prolong the defined interval between COI and the onset of DNS (currently around 40 days). Obviously, such patients would deserve a longer clinical follow-up. On the other hand, these asymptomatic patients with MRI findings warn of the need to dilate such specific follow-up for a period never shorter than the 40 days currently defined.

Another crucial point, a source of variability in the follow-up of these patients and, therefore, in the calculation of the real incidence of DNS, is the lack of uniformity in the follow-up study of patients after COI. In this sense, the follow-up proposal suggested in one of the participating centers (Hospital Universitario Rio Hortega), which proposes the performance of neuroimaging tests complemented with predetermined memory tests if the patient requires them, would represent an option to be evaluated.

The present study also has notable limitations. First, it is a retrospective study, which means that the data were collected from medical records and no prospective follow-up of the patients was carried out. In addition, it is important to highlight the already mentioned low follow-up rate. Because the decision to follow-up patients further was made by the clinicians independently of the study, it is possible that there is a bias in terms of determining the overall incidence of DNS, as those patients who were followed up might have had a higher severity of symptoms that warranted outpatient follow-up. However, it is important to note that this study is the first to describe clinical predictors of the development of DNS in the Spanish population using a cohort design. These findings should serve as a starting point for the development of specific follow-up protocols for patients at risk of developing neurological sequelae after COI in the Spanish population.

Despite the limitations, the high proportion of patients who experience DNS because of COI, with a non-negligible annual incidence and affecting young patients,[8] poses a crucial challenge in clinical practice: predicting the patients at greatest risk of developing DNS. This is especially important for making decisions on the most appropriate treatment and, above all, for planning specific follow-up in a healthcare setting where this follow-up is not standardized.

In conclusion, given the high incidence of DNS after ICO, we consider it essential to establish multidisciplinary clinical protocols for the specific follow-up of these patients. The identification of factors associated with an increased risk of developing DNS should facilitate the early detection of patients requiring specific follow-up after ICO. Low GCS score is a clinical predictor of the development of DNS in the present series.

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