




Original Article

Left-Sided Neurological Symptoms and Negative Diffusion-Weighted MRI in Suspected Minor Stroke Patients

Umberto Pensato^{1,2,3} , Nishita Singh⁴, Raed A. Joundi⁵ , Koji Tanaka³, Andrew M. William Penn⁶, Kristine Votova⁷, Maximilian Bibok⁸, Robert Balshaw⁹, Andrew M. Demchuk^{3,10}, Michael D. Hill^{3,10}  and Shelagh B. Coutts^{3,10}

¹IRCCS Humanitas Research Hospital, Milan, Italy, ²Department of Biomedical Sciences, Humanitas University, Milan, Italy, ³Calgary Stroke Program, Depts of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada, ⁴Department of Internal Medicine (Neurology Division), Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada, ⁵Division of Neurology, Hamilton Health Sciences, McMaster University & Population Health Research Institute, Hamilton, Canada, ⁶Stroke Rapid Assessment Unit, Island Health, Victoria, Canada, ⁷Island Health Regional Health Authority, Division of Medical Sciences, University of Victoria, Victoria, Canada, ⁸Department of Research and Capacity Building, Island Health, Victoria, Canada, ⁹George & Fay Yee Centre for Healthcare Innovation, University of Manitoba, Winnipeg, Canada and ¹⁰Department of Radiology, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada

ABSTRACT: Background: Historically, it has been proposed that functional neurological symptoms occur more frequently on the left side of the body due to a distinct body representation and emotional processing of the right hemisphere, yet objective imaging data to support this are lacking. We aimed to investigate whether patients with acute left-sided symptoms (right hemisphere) suspected of having a minor stroke are more likely to show negative diffusion-weighted imaging (DWI) compared to those with right-sided symptoms. **Methods:** Data are from the SpecTRA (Spectrometry for Transient Ischemic Attack Rapid Assessment) multicenter prospective cohort study conducted between 2013 and 2017. Patients with mild persistent unilateral hemiparesis and/or hemisensory symptoms (National Institute of Health Stroke Scale ≤ 3) and available DWI were included. The primary outcome was the proportion of patients with a negative DWI. **Results:** Of 1731 patients, 584 (30.8%) were included. Of these, 310 (53.1%) patients presented with left-sided symptoms and 274 (46.9%) with right-sided symptoms. Overall, 214 (36.6%) patients had a negative DWI, 126 (58.9%) with left-sided symptoms and 88 (41.1%) with right-sided symptoms: risk ratio (RR) 1.27 (95% CI = 1.02–1.57). Left-sided hemiparesis was associated with negative DWI (RR 1.42 [95% CI = 1.08–1.87]), while left-sided hemisensory symptoms were not (RR 1.11 [95% CI = 0.87–1.41]). There was no effect modification by age or sex on this association ($P_{\text{interaction}}$ 0.787 and 0.057, respectively). **Conclusions:** Unilateral left-sided neurological symptoms were more frequently associated with negative DWI compared to right-sided symptoms in suspected minor stroke patients. This observation is exploratory, as the final diagnosis in DWI-negative cases was not established.

RÉSUMÉ : Symptômes neurologiques du côté gauche et examens d'IRM négatifs pondérés en diffusion chez des patients soupçonnés d'avoir subi un AVC mineur. **Contexte :** Historiquement, il a été proposé que les symptômes neurologiques fonctionnels se produisent plus fréquemment du côté gauche du corps en raison d'une représentation distincte du corps et du traitement émotionnel de l'hémisphère droit. Cela dit, les données objectives d'imagerie pour étayer cette hypothèse font défaut. Nous avons donc cherché à déterminer si les patients présentant des symptômes neurologiques aigus du côté gauche (hémisphère droit) et soupçonnés d'avoir subi un AVC mineur sont plus susceptibles de présenter des résultats négatifs lors d'examen d'IRM pondérés en diffusion que ceux présentant des symptômes du côté droit. **Méthodes :** Les données proviennent de l'étude de cohorte prospective multicentrique SpecTRA (Spectrometry for Transient Ischemic Attack Rapid Assessment) menée entre 2013 et 2017. Les patients présentant une hémiparésie unilatérale persistante légère et/ou des symptômes hémisensoriels (National Institute of Health Stroke Scale [NIHSS] ≤ 3) et des résultats lors d'examen d'IRM pondérés en diffusion ont été inclus. Le résultat principal était la proportion de patients donnant à voir des examens d'IRM négatifs. **Résultats :** Sur 1731 patients, 584 (30,8 %) ont été inclus. Parmi eux, 310 (53,1 %) présentaient des symptômes du côté gauche et 274 (46,9 %) des symptômes du côté droit. Dans l'ensemble, 214 patients (36,6 %) ont donné à voir des examens d'IRM négatifs. De ce nombre, 126 (58,9 %) avaient des symptômes du côté gauche et 88 (41,1 %) des symptômes du côté droit (RR : 1,27 ; IC 95 % = 1,02-1,57). À noter que l'hémiparésie gauche était associée à des examens d'IRM négatifs (RR : 1,42 ; IC 95 % = 1,08-1,87) et que les symptômes hémisensoriels du côté gauche ne l'étaient pas (RR : 1,11 ; IC 95 % = 0,87-1,41). Enfin, il n'y a pas eu de modification de l'effet de l'âge ou du sexe sur cette association (effet d'interaction respectivement de 0,787 et de 0,057). **Conclusions :** Les symptômes neurologiques unilatéraux du côté gauche étaient plus fréquemment associés à des examens d'IRM négatifs que les symptômes du côté droit chez les patients suspectés d'avoir subi un AVC mineur. Cette observation demeure exploratoire, car le diagnostic final dans les cas d'examen d'IRM négatifs n'a pas été établi.

Keywords: functional disorders; ischemic stroke; laterality; psychogenic manifestations; stroke mimics

(Received 8 November 2024; final revisions submitted 21 April 2025; date of acceptance 10 May 2025)

Corresponding author: Shelagh B. Coutts; Email: scoutts@ucalgary.ca

Cite this article: Pensato U, Singh N, Joundi RA, Tanaka K, Penn AMW, Votova K, Bibok M, Balshaw R, Demchuk AM, Hill MD, and Coutts SB. Left-Sided Neurological Symptoms and Negative Diffusion-Weighted MRI in Suspected Minor Stroke Patients. *The Canadian Journal of Neurological Sciences*, <https://doi.org/10.1017/cjn.2025.10125>

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Highlights

- Left-sided motor and sensory symptoms are more frequently associated with negative DWI in patients suspected of minor strokes.
- This finding might be attributed to a distinct body representation and emotional processing of the right hemisphere.
- Further studies are needed to replicate these findings and elucidate the underlying mechanisms

Introduction

Functional neurological disorder (FND) is an umbrella term encompassing several neurological manifestations in which the primary pathophysiological process is a functional, rather than structural, alteration of brain networks.¹ Historically, functional motor or sensory symptoms have been observed more frequently associated with the left side of the body.^{2,3} This phenomenon has been attributed to a distinct body representation and emotional processing of the right hemisphere and a possible “advantage” in the involvement of the non-dominant side.^{2,3} However, contradictory results have emerged from subsequent studies published over two decades ago.²⁻⁴ These studies had several limitations, such as small sample sizes, reporting biases and, most importantly, lack of neuroimaging.²⁻⁴ Therefore, whether there is a laterality preference for functional neurological manifestations remains unclear.

Minor stroke is a subtype of cerebrovascular event characterized by a small cerebral infarct.⁵ More than half of patients initially suspected of having a minor stroke have a final diagnosis of stroke mimic – a condition presenting with stroke-like symptoms but with a nonvascular etiology.^{6,7} FNDs account for about one-third of stroke mimics.⁸ The identification of a brain diffusion-weighted imaging (DWI)-positive lesion is the most reliable indicator of a vascular etiology.^{9,10} Therefore, patients suspected of having an acute minor stroke represent a suitable population to assess the right hemisphere preference of functional disorders, as DWI provides an objective criterion to support the exclusion of an underlying functional etiology.

We aimed to investigate whether patients with unilateral left hemiparesis and/or hemisensory symptoms (implicating the right hemisphere) suspected of having a minor stroke are more likely to be associated with negative DWI compared to those with right hemiparesis and/or hemisensory symptoms (left hemisphere).

Methods

Standard protocol, approvals, registrations and patient consents

Ethics approval was obtained from the relevant ethics committees at all participating centers, and regulatory approval was obtained as necessary. Written informed consent was provided by patients or their authorized representatives.

Patient sample

Data are from the SpecTRA (Spectrometry for Transient Ischemic Attack Rapid Assessment), a multicenter, prospective, observational study that included patients with suspected transient ischemic attack (TIA) or minor stroke between December 2013 and March 2017. The ethics boards at each participating site approved the studies. The methodology and inclusion criteria of the studies have been previously published.^{11,12} In brief, SpecTRA

included patients with mild acute neurological deficit (National Institute of Health Stroke Scale ≤ 3) and referral for neurological examination within 24 hours from symptom onset. Patients with transient monocular blindness or retinal artery occlusion were excluded. All patients were evaluated with either a brain MRI within seven days of the event or a CT and CT angiography within 24 hours. According to local standard protocols, patients were investigated with brain MRI at 1.5 or 3.0 T. A DWI-positive lesion was defined as any region of restricted diffusion consistent with acute ischemic stroke, regardless of anatomical consistency with clinical symptoms. MRIs were completed with 3 mm slice thickness with no gap and were reviewed by a neuroradiologist who was blind to clinical information. Demographics, relevant medical history and baseline clinical features at presentation were collected in each study.

Patients with (i) persistent unilateral motor or sensory symptoms, either in isolation or combined, and (ii) available follow-up DWI MRI were included. Patients with bilateral motor or sensory symptoms, discordant motor and sensory symptoms (i.e., right sensory and left motor symptoms) or symptoms that had resolved at the first neurological examination (time-based TIA) were excluded. Patients with suspected TIA were excluded from this analysis due to the unclear prevalence of FNDs presenting as brief transient episodes and the anticipated higher prevalence of negative DWI in this population.

Assessment of clinical subgroups

Patients were categorized as either having left hemiparesis and/or hemisensory symptoms (right hemisphere) or right hemiparesis and/or hemisensory symptoms (left hemisphere). For further analyses, patients with hemiparesis (\pm hemisensory) were classified as left and right hemiparesis groups, and patients with hemisensory symptoms (\pm hemiparesis) were classified as left and right hemisensory groups. Whenever we mention laterality in the results section, we are referring to the side of the symptoms rather than the hemisphere involved (left-sided symptoms vs. right-sided symptoms). Although brainstem stroke can rarely present with ipsilateral symptoms or a negative DWI, we do not expect these occurrences to significantly affect the analysis due to their anticipated low prevalence.¹³

Outcome

The primary outcome was the proportion of patients with a negative DWI.

Statistical analysis

Continuous variables were presented as medians and interquartile ranges, while categorical variables were reported as counts and percentages. Demographics, medical history and baseline clinical features were compared between patients with left-sided and right-sided symptoms. Univariable comparisons were conducted using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. To assess the association between left-sided and right-sided symptoms and negative DWI, we calculated the risk ratio (RR) with a 95% confidence interval (CI) after constructing a 2×2 contingency table. All analyses were also conducted for patients with motor (left vs. right) and sensory (left vs. right) symptoms. Due to the hypothesis-generating nature of the study, all analyses were considered exploratory and not adjusted for potential confounders.

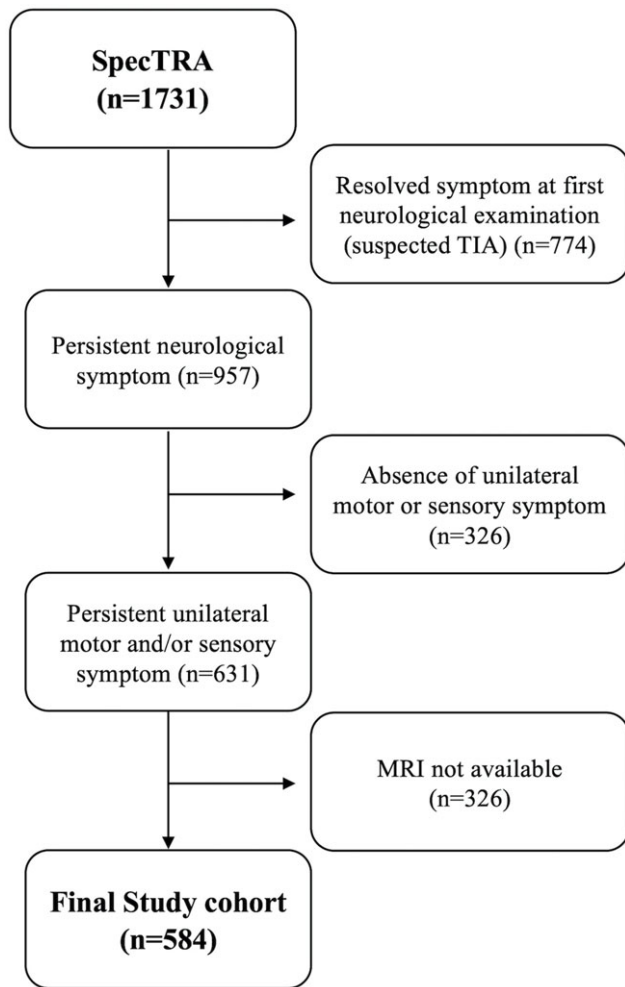


Figure 1. Flowchart of included patients. TIA = transient ischemic attack.

Since younger age and female sex are associated with an increased risk of developing FNDs,^{14,15} we assessed whether the relationship between the symptoms side and the outcome was modified by age or sex by including a two-by-two multiplication interaction term (symptoms side \times age) (symptoms side \times sex) in generalized linear models. Then, we evaluated the significance of the potential effect modification with the $p_{\text{interaction}}$ term. In case of no significant interaction, we provided adjusted estimates of effect using a generalized linear model adjusted for age and sex.

Statistical analyses were performed with Stata (Version 18.0), with all calculated P-values two-tailed and a conventional alpha level of 0.05. Associations were considered statistically significant when the 95% CI did not cross the 1.00 value.

Results

Patient characteristics

Among 1731 enrolled in SpecTRA, 774 patients were excluded due to resolved symptoms at the first neurological examination (suspected TIA), 326 were excluded due to the absence of strictly unilateral motor or sensory symptoms, and 47 were excluded because they were not investigated with acute MRI (Figure 1). Therefore, 584 (30.8%) were included in the final study sample,

and their demographics, medical history and baseline clinical features are summarized in Table 1. Overall, 310 (53.1%) patients presented with left-sided symptoms and 274 (46.9%) with right-sided symptoms. Compared to patients with right-sided symptoms, patients who presented with left-sided symptoms were younger (67.1 [IQR = 56–77] years vs. 69.8 [IQR = 60–80] years, $p = 0.042$), exhibited a lower prevalence of arterial hypertension (51.6% [$n = 150$] vs. 62% [$n = 170$], $p = 0.012$) and coronary artery disease (8.7% [$n = 27$] vs. 15.3% [$n = 42$], $p = 0.015$) and experienced hemisensory symptoms more frequently (66.5% [$n = 206$] vs. 55.5% [$n = 152$], $p = 0.008$).

Association between symptoms laterality and outcomes

Overall, 214 (36.6%) patients had a negative DWI. Among patients with negative DWI, 126 (58.9%) presented with left-sided symptoms and 88 (41.1%) with right-sided symptoms ($p = 0.039$) (Figure 2). There was a significant association between left-sided symptoms and negative DWI: RR 1.27 (95% CI = 1.02–1.57) (Table 2). Among the 370 patients with a positive DWI, 184 (49.7%) presented with left-sided symptoms and 186 (50.3%) with right-sided symptoms. Results were similar in a sensitivity analysis where patients with aphasia at baseline were excluded (Supplementary Material 1).

Subgroup analyses in motor and sensory symptoms

In the subgroup with hemiparesis ($n = 468$), 149 (31.8%) had a negative DWI. Among them, 89 (59.7%) presented with left-sided hemiparesis and 60 (40.3%) with right-sided hemiparesis ($p = 0.013$) (Figure 2). There was a significant association between left-sided hemiparesis and negative DWI: RR 1.42 (95% CI = 1.08–1.87) (Table 2).

In the subgroup with hemisensory symptoms ($n = 358$), 155 (43.3%) had a negative DWI. Among them, 93 (60%) presented with left-sided hemisensory symptoms and 62 (40%) with right-sided hemisensory symptoms ($p = 0.451$) (Figure 2). There was no significant association between left-sided hemisensory symptoms and negative DWI: RR 1.11 (95% CI = 0.87–1.41) (Table 2).

Effect of age and sex on the association between symptom laterality and DWI negativity

The estimated probability of negative DWI decreased steadily with advancing age (OR 0.98 [95% CI = 0.97–0.99] per 1-year increase), yet there was no interaction effect between age and the outcome concerning left or right symptoms ($p_{\text{interaction}} = 0.787$) (Figure 3).

In females ($n = 258$), 121 (46.9%) had a negative DWI. Among them, 73 (60.3%) presented with left-sided symptoms and 48 (39.7%) with right-sided symptoms ($p = 0.132$). In males ($n = 326$), 93 (28.5%) had a negative DWI. Among them, 53 (57%) presented with left-sided symptoms, and 40 (43%) with right-sided symptoms ($p = 0.222$). There was no interaction effect between sex and the outcome concerning left-sided or right-sided symptoms ($p_{\text{interaction}} = 0.057$). After adjustments for age and sex, there was no association between left-sided symptoms and negative DWI (RR 1.16 (95% CI = 0.95–1.43).

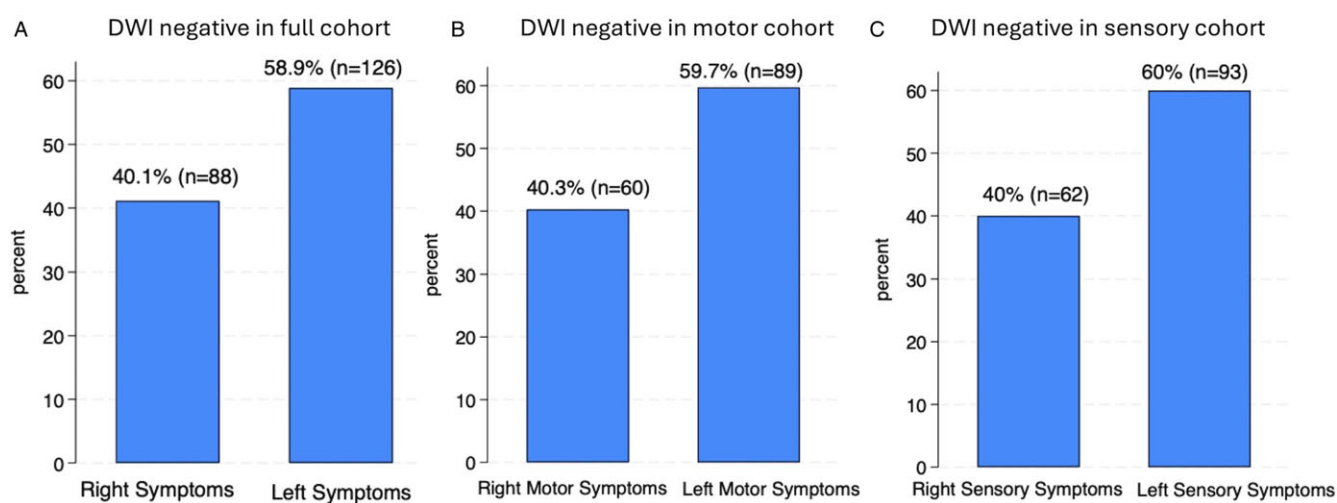
Discussion

In our study, unilateral acute left-sided hemiparesis and/or hemisensory symptoms, compared with right-sided symptoms, were more frequently associated with negative DWI in a

Table 1. Comparison of demographics, medical history, baseline clinical features and outcomes between left and right groups

	Full cohort (n = 584)	Left symptoms (n = 310)	Right symptoms (n = 274)	P-value
Demographics				
Age (years) (median, IQR)	68.5 (57.9–78.2)	67.1 (56–77)	69.8 (60–80)	0.042
Sex (females) (n, %)	258 (44.2%)	142 (45.8%)	116 (42.3%)	0.405
Medical history				
Current smoking (n, %)	82 (14.0%)	40 (12.9%)	42 (15.3%)	0.406
Arterial hypertension (n, %)	330 (56.5%)	150 (51.6%)	170 (62%)	0.012
Diabetes mellitus (n, %)	103 (17.4%)	52 (16.8%)	51 (18.6%)	0.587
Atrial Fibrillation (n, %)	66 (11.3%)	31 (10%)	35 (12.8%)	0.298
History of stroke (n, %)	56 (9.6%)	34 (11%)	22 (8%)	0.261
Coronary artery disease (n, %)	69 (11.8%)	27 (8.7%)	42 (15.3%)	0.015
Migraine with aura (n, %)	71 (12.2%)	39 (12.6%)	32 (11.7%)	0.8
Baseline Clinical features				
Systolic Blood pressure (mmHg) (median, IQR)	146 (129–164)	143 (127–160)	147 (132–170)	0.121
Hemiparesis (n, %)	468 (80.1%)	239 (77.1%)	229 (83.6%)	0.061
Hemisensory symptoms (n, %)	358 (61.3%)	206 (66.5%)	152 (55.5%)	0.008
Speech abnormalities (n, %)	270 (46.2%)	135 (43.6%)	135 (49.3%)	0.184
Headache (n, %)	187 (37%)	100 (32.3%)	87 (31.8%)	0.929
Chest pain (n, %)	18 (3.1%)	14 (4.5%)	4 (1.5%)	0.052
Anxiety (n, %)	32 (5.5%)	18 (5.8%)	14 (5.1%)	0.856
Time features				
Onset-to-presentation time (hours) (median, IQR)	11 (5–17)	12 (5–18)	11 (5–16)	0.829
Onset-to-MRI time (hours) (median, IQR)	17 (7–29)	17 (7–27)	20 (8–29)	0.162

IQR = interquartile interval.

**Figure 2.** Distribution of laterality in patients with negative diffusion-weighted MRI in the full cohort (A), the subgroup with hemiparesis (B) and the subgroup with hemisensory symptoms (C). DWI = diffusion-weighted imaging.

population of suspected minor strokes, showing an increased probability of approximately one-third. These findings were mainly driven by the presence of motor symptoms and were consistent across different ages and sexes.

In our study sample, the proportion of patients presenting with acute left-sided symptoms was slightly higher than those with right-sided symptoms (~53% vs. ~47%). While previous studies have shown a higher overall prevalence of right-sided symptoms

Table 2. Left symptoms and association with negative DWI

	Patients (n)	Negative DWI (n, %)	RR (95% CI)
Left-sided hemiparesis or hemisensory symptoms	310	126 (40.6%)	1.27 (1.02–1.57)
Left-sided hemiparesis	239	89 (37.2%)	1.42 (1.08–1.87)
Left-sided hemisensory symptoms	206	93 (45%)	1.11 (0.87–1.41)
Right-sided hemiparesis or hemisensory symptoms	274	88 (32.1%)	0.79 (0.64–0.98)
Right-sided hemiparesis	229	60 (26.2%)	0.70 (0.54–0.92)
Right-sided hemisensory symptoms	152	62 (40.8%)	0.90 (0.71–1.15)

DWI = diffusion-weighted imaging; RR = risk ratio; CI = confidence interval.

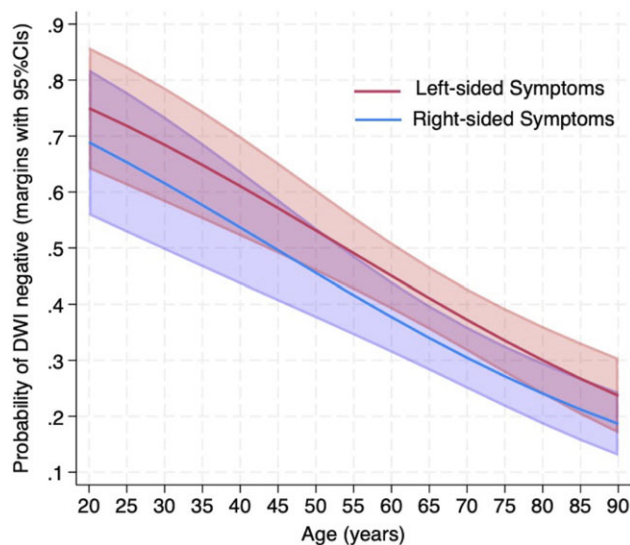


Figure 3. Predicted probability of negative diffusion-weighted imaging as a function of age in patients with left versus right symptoms. DWI = diffusion-weighted imaging.

among stroke patients,^{16,17} an opposite trend has been observed in the distinctive subgroup of minor strokes.^{18,19} These findings can be explained by the higher clinical eloquence of the left hemisphere, which facilitates diagnosis (high prevalence overall) but, at the same time, translates into greater clinical severity (low prevalence in the minor stroke subgroup).^{18,20,21} However, in our study, the proportion of patients with positive DWI was equally balanced (~50%), in contrast with the proportion with negative DWI (~60% vs. ~40%). This supports the concept that the difference we observed in symptoms laterality was mainly driven by stroke mimics rather than true acute strokes.

The underpinning biology of the laterality preference in DWI-negative patients remains uncertain. This group includes stroke mimics and possibly a small representation of true acute strokes without lesions (TIAs).²² Among stroke mimics, there is little to no evidence for a laterality preference. The higher clinical eloquence and greater metabolic demand of the left hemisphere might suggest a lower resilience and a lower clinical threshold for detecting mimics in the left hemisphere. For instance, hypoglycemia-

induced hemiparesis is twice as common with right-sided symptoms.²³ In other words, the minimal evidence available supports a preference for right symptoms in stroke mimics rather than left symptoms. Conversely, functional disorders have been consistently associated with a preference for left-sided symptoms.^{2,3}

There are several potential explanations for this latter phenomenon, which are not mutually exclusive. First, left-sided symptoms represent one of the heralding presentations of acute coronary syndromes due to the distinctive sensory innervation of the heart.²⁴ This might result in an overrepresentation of left upper arm symptoms in anxious individuals who fear they are experiencing a myocardial infarction. Second, there might be a functional advantage in presenting symptoms on the non-dominant side, which is the left side for the vast majority of individuals.³ Third, differences in attention or perception of disability in the dominant side might have influenced the outcome. Finally, the right hemisphere is believed to play a more significant role in the mediation of affective or motivationally determined somatic symptoms and has a different spatial representation of the body in comparison to the left hemisphere.^{2,3}

In our cohort, in the subgroup analyses, the left-sided preference in patients with negative DWI was observed only in those with motor symptoms, but not in those with sensory symptoms. The underlying reasons for this observation remain unclear, yet it is possible that while sensory symptoms are more commonly associated with functional disorders,¹ the different body laterality might be more pronounced in motor symptoms. Moreover, the smaller number of patients presenting with sensory symptoms may have limited the ability to detect a statistically significant difference.

Our findings should be interpreted as exploratory, and several limitations must be acknowledged. First, DWI negativity does not fully exclude a vascular etiology,²² and second, we did not evaluate for FNDs. Current diagnostic criteria for FND emphasize the need for positive rule-in signs on neurological exam (e.g., incongruence with known neurological disease, inconsistency and variability, improvement with distraction or automatic movements) and not simply normal imaging.¹⁴ Moreover, FND can co-occur with structural disease, including stroke, in a minority of cases.²⁵ Finally, a variety of alternative diagnoses to functional and vascular disorders are also possible, including neurological (e.g., spinal cord pathologies and neuropathies) or non-neurological (e.g., acute coronary syndrome) conditions. Third, hand dominance or a comprehensive assessment of hemisphere dominance was not collected. Fourth, ethnic differences might influence the clinical presentation of functional disorders. Fifth, multiple subgroup analyses might have increased the risk of type I error in our study. Finally, we defined suspected minor stroke on the persistence of neurological symptoms at the initial medical examination. This pragmatic definition aimed to reduce the proportion of ischemic strokes with negative DWI. However, there was no restriction on the minimum duration from symptom onset, so some TIA patients were likely included.

Notably, our study aims to explain the laterality preference of DWI-negative patients, not to inform diagnostic or therapeutic decision-making in the emergency department.

Conclusion

Unilateral acute left-sided hemiparesis or hemisensory symptoms, compared to right-sided symptoms, were more frequently

associated with DWI negativity in a population of suspected minor strokes, with an increased probability of approximately one-third. These findings were mainly driven by the presence of motor symptoms and were consistent across different ages and sexes. Our observations are exploratory, and future studies are needed to replicate them in another cohort and explore the many possible causes driving the relationship between left-sided neurological symptoms and DWI negativity, including FNDs.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/cjn.2025.10125>.

Acknowledgments. None.

Author contributions. UP drafted the manuscript, conceived the study and performed the statistical analysis. NS, RAD, KT, AMP, KV, MMBB, RBF, AMD, MDH and SBC collected the data, revised the manuscript for content, interpreted the results and supervised the study.

Funding statement. The original SpecTRA was supported by Genome British Columbia, Genome Alberta and Genome Canada (grant no. TIA 4125-Penn).

Competing interests. None.

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