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Incontinence and gait disturbance after intraventricular extension of intracerebral hemorrhage

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ABSTRACT

Objective: We tested the hypothesis that intraventricular hemorrhage (IVH) is associated with incontinence and gait disturbance among survivors of intracerebral hemorrhage (ICH) at 3-month follow-ups.

Methods: The Genetic and Environmental Risk Factors for Hemorrhagic Stroke study was used as the discovery set. The Ethnic/Racial Variations of Intracerebral Hemorrhage study served as a replication set. Both studies performed prospective hot-pursuit recruitment of ICH cases with 3-month follow-up. Multivariable logistic regression analyses were computed to identify risk factors for incontinence and gait dysmobility at 3 months after ICH.

Results: The study population consisted of 307 ICH cases in the discovery set and 1,374 cases in the replication set. In the discovery set, we found that increasing IVH volume was associated with incontinence (odds ratio [OR] 1.50; 95% confidence interval [CI] 1.10–2.06) and dysmobility (OR 1.58; 95% CI 1.17–2.15) after controlling for ICH location, initial ICH volume, age, baseline modified Rankin Scale score, sex, and admission Glasgow Coma Scale score. In the replication set, increasing IVH volume was also associated with both incontinence (OR 1.42; 95% CI 1.27–1.60) and dysmobility (OR 1.40; 95% CI 1.24–1.57) after controlling for the same variables.

Conclusion: ICH subjects with IVH extension are at an increased risk for developing incontinence and dysmobility after controlling for factors associated with severity and disability. This finding suggests a potential target to prevent or treat long-term disability after ICH with IVH.
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GLOSSARY

CI = confidence interval; **ERICH** = Ethnic/Racial Variations of Intracerebral Hemorrhage; **GCS** = Glasgow Coma Scale; **GERFHS** = Genetic and Environmental Risk Factors for Hemorrhagic Stroke; **ICH** = intracerebral hemorrhage; **IVH** = intraventricular hemorrhage; **mRS** = modified Rankin Scale; **OR** = odds ratio; **SBP** = systolic blood pressure.

Intracerebral hemorrhage (ICH) is responsible for 10%–15% of strokes worldwide each year.[1] Patients who experience ICH have the highest short- and long-term morbidity and mortality rates among the major stroke subtypes.[2,3] Rupture of hemorrhage into the ventricles increases mortality to 50%–80% and doubles the rate of poor functional outcome among survivors at hospital discharge compared with those without intraventricular hemorrhage (IVH).[4–7] Beyond the acute period, the presence of IVH also worsens long-term outcome.[8,9]

In ventricular disease, stretching the periventricular white matter tracks, especially the anterior corona radiata, is proposed as the mechanism for development of incontinence and gait instability.[10,11] Therefore, we hypothesized that IVH causes urinary incontinence and gait disturbance, contributing to worse functional outcomes.

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Figure 1 Flow diagram of subject inclusion/exclusion

Discovery cohort - GERFHS	Replication cohort - ERICH
ICH cases (N=534)	ICH cases (N=2276)
↓	↓
Died before 3-month follow-up (n=80)	Died before 3-month follow-up (n=450)
Prestroke mRS ≥4 (n=22)	Prestroke mRS ≥4 (n=47)
Lost to follow-up (n=108)	Lost to follow-up (n=301)
No volume data (n=13)	No volume data (n=90)
No Barthel data at follow-up (n=4)	No Barthel data at follow-up (n=14)
↓	↓
ICH cases that met criteria (n=307)	ICH cases that met criteria (n=1374)

ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage; GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke; ICH = intracerebral hemorrhage; mRS = modified Rankin Scale.

METHODS Methods for the Genetic and Environmental Risk Factors for Hemorrhagic Stroke (GERFHS) and the Ethnic/Racial Variations of Intracerebral Hemorrhage (ERICH) studies have been published previously.[12,13] Briefly, the GERFHS study prospectively recruited cases of spontaneous ICH and matched controls from the Greater Cincinnati/Northern Kentucky geographic region. This study then served as the model for the ERICH study, a multicenter case-control study of ICH at 19 centers throughout the United States. The 2 studies have similar protocols and data collection forms.

Standard protocol approvals, registrations, and patient consents. Institutional review boards from all participating centers approved the protocols and all participants or their legally authorized representative provided informed consent to participate.

As the main hypothesis related to incontinence and gait dysfunction at follow-up, patients who had died prior to follow-up were excluded from analysis as well as patients who had a prestroke modified Rankin Scale (mRS) score of 4 or higher. As the volume of ICH and IVH was required, those without imaging available or with motion artifact obscuring assessment were also removed. Finally, those lost to follow-up or who did not complete the Barthel index portion of the follow-up were excluded.

CT images on admission and during the subject's inpatient stay were analyzed for ICH volume and location as well as IVH presence and volume by a single reviewer for GERFHS (A.J.K.) and at a central neuroimaging core for ERICH blinded to clinical evaluations. ICH and IVH volumes were measured using ABC/2 in GERFHS and planimetric analysis in ERICH.[14,15] Glasgow Coma Scale (GCS) score was obtained upon initial presentation to the emergency department. We used the 3-month Barthel Index subscores to define incontinence (<10 for bladder) and dysmobility (<15 for mobility).[16,17] We used the mRS to ascertain the patient's prestroke and 3-month function.[18]

Statistical analysis. We present descriptive statistics as means with SDs for continuous variables and as frequencies with percentages for categorical variables. Median and interquartile range are presented for GCS at admission. The ICH and IVH volumes were heavily skewed and were natural logarithmically ($\log_e$) transformed to best approximate distributional assumptions. Two-sample t tests were used to compare age and ICH volume between those with and without IVH. Wilcoxon rank-sum tests were used to compare admission GCS, Cochran-Armitage trend test was used to compare prestroke mRS, and a χ^2 test for contingency tables was computed to compare sex, anticoagulant use, hypertension, location of ICH, incontinence at 3 months, and dysmobility at 3 months. We computed univariable logistic regression to model incontinence and dysmobility using all variables listed above. We used backward elimination to construct multivariable logistic regression models, and all variables with $p \leq 0.05$ were retained. Standard regression diagnostics for influence, collinearity, and model fit were examined routinely. Here, the condition index (i.e., the square root of the ratio of the largest to smallest eigenvalue of the design matrix) $\kappa = 15.4$ and the range of variance inflation factors was 1.03–1.56. These values are within the acceptable range and do not indicate significant collinearity. The computed Hosmer & Lemeshow goodness-of-fit test found no evidence of a significant lack of fit in any of the reported models ($p \geq 0.20$). Meta-analyses were computed using the weighted inverse normal method, weighting by the sample size.[19]

RESULTS Figure 1 shows the loss of subjects by inclusion criteria for each cohort of studies. The lack of imaging data occurred primarily because of either motion artifact on baseline scan or the subject presented to a hospital outside of a recruiting center and attempts to obtain the original image failed. The discovery cohort enrolled 534 cases of spontaneous ICH and the replication cohort enrolled 2,276; 307 and 1,374 cases, respectively, met inclusion criteria.

Table 1 presents the demographic variables for the 2 cohorts divided by presence of IVH. Compared with patients without IVH, those with IVH more commonly had a deep ICH location, had greater ICH volume, and had diminished consciousness on admission as measured by GCS. In the discovery set, the cases with IVH were slightly younger than those without, but this difference did not replicate. In the replication set, hypertension was slightly more common among those with IVH, although this difference was not significant in the discovery set.

In both the discovery and replication sets, approximately 40% of patients with IVH had incontinence at 3 months compared with approximately 20% of those without IVH. Gait dysfunction occurred in approximately half of cases with IVH compared with roughly a third of those without IVH in both the discovery and replication sets.

Given that incontinence and dysmobility may occur as a result of deficits related to the ICH or age, we performed multivariable logistic regression modeling to determine whether IVH was an independent risk factor for incontinence and dysmobility. Table 2 shows the results of the models performed separately for the GERFHS and ERICH studies. In both the discovery and replication sets, the presence of IVH was associated with an independent risk of both incontinence and dysmobility with similar point

Table 1 Baseline patient demographics and univariable comparison for incontinence and gait impairment at 3 months

	GERFHS: Discovery set			ERICH: Replication set		
	IVH present (n = 105)	IVH absent (n = 202)	*p* Value	IVH present (n = 518)	IVH absent (n = 856)	*p* Value
Age, y, mean (SD)	66.3 (13.5)	69.9 (13.2)	0.026	59.4 (13.7)	59.8 (13.7)	0.57
Female, n (%)	45 (42.9)	92 (45.5)	0.65	204 (39.4)	340 (39.7)	0.90
GCS at presentation, median (IQR)	15 (13–15)	15 (14–15)	0.001	14 (10–15)	15 (14–15)	<0.001
Anticoagulant use, n (%)	16 (15.2)	23 (11.4)	0.34	45 (8.7)	79 (9.2)	0.73
Hypertension, n (%)	76 (73.8)	143 (71.5)	0.67	455 (88.0)	716 (83.6)	0.03
ICH volume, mean (95% CI)	14.0 (11.4–17.2)	7.5 (6.3–9.0)	<0.001	10.2 (9.2–11.3)	7.7 (7.1–8.4)	<0.001
Location, n (%)						
Lobar	32 (30.5)	90 (44.6)		108 (20.9)	315 (36.8)	
Deep	63 (60.0)	84 (41.6)		341 (65.8)	413 (48.3)	
Brainstem	1 (0.9)	11 (5.5)		11 (2.1)	55 (6.4)	
Cerebellar	9 (8.6)	17 (8.4)		35 (6.8)	73 (8.5)	
Primary IVH	0	0	0.008	23 (4.4)	0 (0)	<0.001
mRS before ICH, median (IQR)	0 (0–1)	0 (0–1)	0.0478	0 (0–0)	0 (0–0)	0.6880
Incontinence at 3 months, n (%)	42 (40.0)	46 (22.8)	0.002	206 (39.8)	174 (20.3)	<0.001
Difficulty with mobility at 3 months, n (%)	51 (48.6)	55 (27.2)	<0.001	294 (56.8)	289 (33.8)	<0.001

Abbreviations: CI = confidence interval; ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage; GCS = Glasgow Coma Scale; GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke; ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale.

estimates. This association was independent of volume or location of ICH, presenting severity based on GCS, prestroke disability, and patient age, all of which were also predictors of incontinence and dysmobility. In the ERICH cohort, female sex was also independently associated with incontinence (odds ratio [OR] 1.51; 95% confidence interval [CI] 1.2–2.0; $p = 0.004$) and dysmobility (OR 1.68; 95% CI 1.3–2.2; $p = 0.0001$), but that association was not found in the GERFHS study. We also evaluated the effect of race in the ERICH cohort and found in univariable analysis that African American patients were slightly more likely to have IVH, but once controlling for the other predictors of IVH (including greater deep location of ICH), the association was not significant in multivariable analysis. Figure 2 presents the meta-analysis for the volume of IVH to incontinence and dysmobility, which demonstrates a consistent effect across both studies.

In GERFHS, in univariate analysis, subjects with initial systolic blood pressures (SBP) of <140 mm Hg had a better outcome when it came to incontinence than those with SBP >140 mm Hg (OR 1.90; 95% CI 1.12–3.21; $p = 0.0174$). When included in the multivariate model for incontinence, the final model was unchanged. There was no significant difference for dysmobility (OR 1.23; 95% CI 0.78–2.00; $p = 0.405$). There was no significant difference in outcomes based on initial SBP for the ERICH cohort: incontinence (OR 1.05; 95% CI 0.83–1.33; $p = 0.695$) and dysmobility (OR 0.94; 95% CI 0.76–1.17; $p = 0.560$).

We sought to determine whether subjects who were excluded from the analysis due to loss to follow-up or missing outcome responses were more or less disabled (with incontinence and gait dysfunction) at baseline than the included patients in order to assess inclusion bias. We compared the excluded cases from the included cases in both the discovery and replication sets (table 3). The excluded subjects were more severely affected and had a greater frequency of other risk factors associated with incontinence and gait dysfunction rather than a lower frequency; thus, our findings were unlikely to be the result of inclusion bias, which for our cohort would bias the result towards the null.

There were 2 subjects in GERFHS who received intraventricular thrombolytic injections. Neither was incontinent and one had dysmobility. There were 29 subjects in ERICH who received thrombolytic injections, and one subject without information on thrombolytics. Of those, 15 of 29 were incontinent compared to 365 of 1,344 who did not have thrombolytic injection ($p = 0.003$). Additionally, 19 of the 29 were classified as having

Table 2 Multivariable independent predictors of 3-month incontinence or dysmobility

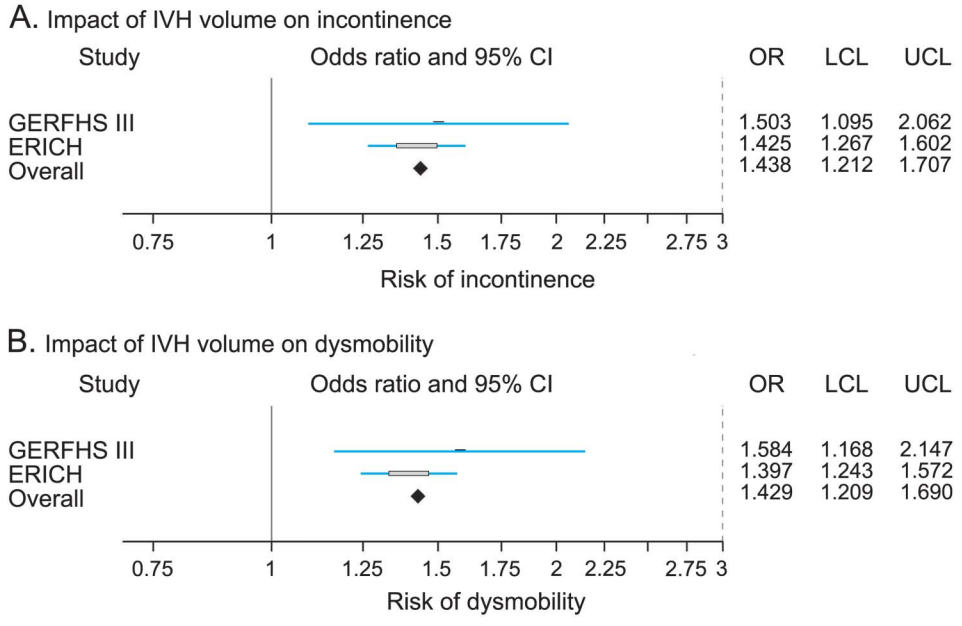
	GERFHS: Discovery set				ERICH: Replication set			
	Incontinence		Dysmobility		Incontinence		Dysmobility	
Variables	OR (CI)	*p* Value	OR (CI)	*p* Value	OR (CI)	*p* Value	OR (CI)	*p* Value
IVH volume	1.50 (1.10-2.06)	0.0117	1.58 (1.17-2.15)	0.0031	1.42 (1.27-1.60)	<0.0001	1.40 (1.24-1.57)	<0.0001
Age (per year)	1.07 (1.04-1.10)	<0.0001	1.06 (1.03-1.09)	<0.0001	1.04 (1.03-1.05)	<0.0001	1.04 (1.03-1.05)	<0.0001
ICH volume	1.78 (1.25-2.54)	0.0015	1.85 (1.32-2.60)	0.0004	1.77 (1.51-2.06)	<0.0001	2.22 (1.91-2.58)	<0.0001
Location								
Lobar	0.33 (0.15-0.72)	0.005	0.18 (0.09-0.40)	<0.0001	0.51 (0.36-0.72)	0.0001	0.27 (0.19-0.37)	<0.0001
Deep	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Brainstem	5.22 (1.05-25.95)	0.043	1.84 (0.35-9.62)	0.4712	3.39 (1.83-6.29)	0.0001	3.71 (2.06-6.69)	<0.0001
Cerebellar	1.73 (0.62-4.83)	0.30	1.48 (0.55-3.99)	0.4419	0.70 (0.41-1.20)	0.19	0.77 (0.48-1.24)	0.28
Primary IVH					1.72 (0.58-5.03)	0.33	1.54 (0.55-4.32)	0.42
GCS at presentation (per point)	0.89 (0.77-1.03)	0.1198	0.88 (0.76-1.03)	0.1020	0.90 (0.87-0.94)	<0.0001	0.88 (0.84-0.93)	<0.0001
mRS before ICH	1.65 (1.24-2.18)	0.0006	1.71 (1.29-2.26)	0.0002	1.62 (1.38-1.91)	<0.0001	1.45 (1.22-1.71)	<0.0001
Female	1.42 (0.79-2.57)	0.2412	0.99 (0.56-1.75)	0.9648	1.51 (1.15-2.00)	0.0036	1.68 (1.29-2.18)	0.0001

Abbreviations: CI = confidence interval; ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage; GCS = Glasgow Coma Scale; GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale; OR = odds ratio.

dysmobility compared to 564 out of 1,344 without thrombolytic injection ($p = 0.011$).

DISCUSSION In this secondary analysis of 2 independently recruited ICH cohorts, we report an association between IVH, incontinence, and gait difficulty 3 months after ICH that was independent of the known predictors of ICH severity including volume and location of ICH, age, GCS at presentation, and prestroke disability. These findings may explain the contribution towards worse long-term functional outcomes in ICH patients with IVH

Figure 2 Meta-analysis of effect of intraventricular hemorrhage (IVH) volume on incontinence and dysmobility at 3 months after intracerebral hemorrhage (ICH)



(A) Incontinence and (B) dysmobility at 3 months after ICH. CI = confidence interval; ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage; GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke; LCL = lower confidence limit; OR = odds ratio; UCL = upper confidence limit.

Table 3 Follow-up cases vs excluded cases

	GERFHS			ERICH		
	Included (n = 307)	Excluded (n = 125)	*p* Value	Included (n = 1,374)	Excluded (n = 315)	*p* Value
Age, y, mean (SD)	68.7 (13.4)	72.5 (13.6)	0.008	59.7 (13.7)	60 (13.3)	0.73
Female, n (%)	137 (44.6)	64 (51.2)	0.21	544 (39.6)	123 (39.1)	0.86
GCS at presentation, median (IQR)	15 (14–15)	14 (12–15)	<0.001	15 (13–15)	15 (13–15)	0.38
Anticoagulant use, n (%)	39 (12.7)	12 (9.6)	0.36	124 (9)	19 (6)	0.09
Hypertension, n (%)	242 (79.3)	101 (80.8)	0.73	1,171 (85.3)	258 (82.2)	0.17
ICH volume, geometric mean (95% CI)	9.3 (8.1–10.7)	17.9 (14.0–22.9)	<0.001	8.6 (8.0–9.1)	7.9 (6.9–9.1)	0.31
Presence of IVH, n (%)	105 (34.2)	57 (52.3)	<0.001	518 (37.7)	111 (35.2)	0.41
IVH volume, geometric mean (95% CI)	0.9 (0.7–1.1)	2.0 (1.3–2.7)	<0.001	1.1 (1.0–1.3)	1.0 (0.8–1.3)	0.51
mRS before stroke, n (%)			0.009			0.18
0	198 (64.5)	61 (49.2)		1,056 (76.9)	228 (72.4)	
1	44 (14.3)	18 (14.5)		150 (10.9)	47 (14.9)	
2	25 (8.1)	16 (12.9)		120 (8.7)	26 (8.3)	
3	40 (13.0)	29 (23.4)		48 (3.5)	14 (4.4)	
Location, n (%)						
Lobar	122 (39.7)	56 (44.8)	0.51	368 (26.8)	72 (22.9)	0.19
Deep	147 (47.9)	59 (47.2)		801 (58.3)	197 (62.5)	
Brainstem	12 (3.9)	4 (3.2)		65 (4.7)	20 (6.4)	
Cerebellum	26 (8.5)	6 (4.8)		108 (7.9)	23 (7.3)	
Pure IVH				32 (2.3)	3 (1.0)	

Abbreviations: CI = confidence interval; ERICH = Ethnic/Racial Variations of Intracerebral Hemorrhage; GCS = Glasgow Coma Scale; GERFHS = Genetic and Environmental Risk Factors for Hemorrhagic Stroke; ICH = intracerebral hemorrhage; IQR = interquartile range; IVH = intraventricular hemorrhage; mRS = modified Rankin Scale.

compared to those without IVH after accounting for ICH severity.[20–23]

While association does not equal causation, other ventricular diseases with similar findings include subarachnoid hemorrhage, in which involvement of the ventricles was associated with incontinence, as well as normal-pressure hydrocephalus, in which incontinence and gait disability are common features.[24,25] Chronic pressure on periventricular white matter tracks by IVH and presumably hydrocephalus may lead to damage, degeneration, and potentially irreversible disability.[26–28] However, damage may be reversible, as diffusion tensor imaging changes in corticospinal tracts of patients with hydrocephalus normalized after treatment with shunt surgery.[26] Further, similar improvements in diffusion tensor imaging parameters of periventricular white matter tracts after acute hydrocephalus have been reported with shunting in patients with IVH.[27] Long-term shunt placement has proven effective in the treatment of ventricular-related diseases, including normal-pressure hydrocephalus.[29,30]

A limitation of the current analysis is that long-term follow-up brain imaging was not obtained as part of these epidemiologic studies, so we cannot determine which subjects developed ventricular enlargement and whether that was associated with the higher rates of incontinence and gait dysmobility. Additionally, hematoma expansion was not recorded as a variable and thus represents a potential confounder. The Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) study tests the hypothesis that intraventricular injection of thrombolytic agents will improve long-term outcome and will specifically evaluate the rate of ventricular enlargement.[31] If effective in reducing hydrocephalus, the study may also evaluate whether the effect improves specifically the rate of subsequent incontinence and gait disability. After aneurysmal subarachnoid hemorrhage with incontinence and cognitive dysfunction, treatment with ventriculoperitoneal shunt improved outcomes compared to rehabilitation alone.[24]

Strengths of the present evaluation include replication of the original findings in an independent cohort. Cases were prospectively recruited from both

a population-based case-control study of ICH as well as from a multicenter, multiethnic study of ICH, and showed remarkably similar effect sizes and distributions despite differences in study designs. Finally, sample size affords considerable power allowing for the adjustment of numerous clinical variables including both injury severity markers and factors associated with incontinence or disability. Imaging was evaluated centrally and blinded to clinical presentation variables or outcome.

We used the Barthel Index to identify the presence of incontinence and gait dysmobility. Because the index relies on self-report, potential reporting bias exists. However, this bias should exist equally for patients with and without IVH. Unless patients or their proxies suspected that IVH were somehow related to these symptoms, reporting bias seems unlikely. We were unable to compare the incidence of incontinence and gait disturbance between included and excluded subjects because of a lack of data regarding these endpoints due to death or lack of follow-up. Finally, the difference in baseline variables between subjects included in this analysis vs those excluded (primarily due to loss to follow-up) is a potential limitation. Thus, we evaluated whether differences in baseline variables existed. In the GERFHS cohort, excluded cases were more likely to be older, have lower GCS, have greater ICH volume, have higher proportion of IVH, and be disabled prior to stroke. However, those exclusions would bias towards the excluded population being more likely to have incontinence and gait disability and therefore would bias towards the null. In the ERICH cohort, no significant differences were observed between the excluded and included cases with respect to all of the major variables examined. Thus, it is unlikely that selection bias led to the findings identified.

We report an association between presence of IVH and incontinence and gait dysmobility at 3-month follow-up in 2 independent cohorts of ICH. This finding may help to explain why long-term disability rates continue to be higher after IVH even after controlling for other clinical variables of severity and presumed resolution of the IVH. Future studies should seek to confirm ventricular dilation among those with IVH and investigate its association with incontinence and dysmobility and active screening for these symptoms among ICH cases with IVH should be considered.

AUTHOR CONTRIBUTIONS

Daniel Woo: drafting/revising the manuscript, study concept/design, and interpretation of data. Andrew J. Kruger: drafting/revising the manuscript, study concept/design, and interpretation of data. Padmini Sekar: drafting/revising the manuscript, study concept/design, and interpretation of data. Mary Haverbusch: drafting/revising the manuscript, study concept/design, and interpretation of data. Jennifer Osborne: drafting/revising the manuscript, study concept/design, and interpretation of data. Charles J. Moomaw: drafting/revising the manuscript, study concept/design, and interpretation of data. Sharyl Martini: drafting/revising the manuscript, study concept/design, and interpretation of data. Shahla M. Hosseini: drafting/revising the manuscript, study concept/design, and interpretation of data. Simona Ferioli: drafting/revising the manuscript, study concept/design, and interpretation of data. Bradford B. Worrall: drafting/revising the manuscript, study concept/design, and interpretation of data. Mitchell S.V. Elkind: drafting/revising the manuscript, study concept/design, and interpretation of data. Gene Sung: drafting/revising the manuscript, study concept/design, and interpretation of data. Michael James: drafting/revising the manuscript, study concept/design, and interpretation of data. Fernando D. Testai: drafting/revising the manuscript, study concept/design, and interpretation of data. Carl D. Langefeld: drafting/revising the manuscript, study concept/design, and interpretation of data. Joseph P. Broderick: drafting/revising the manuscript, study concept/design, and interpretation of data. Sebastian Koch: drafting/revising the manuscript, study concept/design, and interpretation of data. Matthew L. Flaherty: drafting/revising the manuscript, study concept/design, and interpretation of data.

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DISCLOSURE

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Incontinence and gait disturbance after intraventricular extension of intracerebral hemorrhage

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