ONLINE SUPPLEMENTAL MATERIAL

Neurologic Outcome Predictors in Pediatric Intracerebral Hemorrhage: A Prospective Study

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Supplemental Methods
Pediatric Intracerebral Hemorrhage Standard Acute Evaluation

Given the observational nature of this study, a specific protocol was not created to guide the care of enrolled children. Practices across the institutions, however, varied minimally. A standard evaluation is described here for a more thorough presentation of methodology.

Case ascertainment was facilitated by prior implementation of a protocol for children suspected to have an intracerebral hemorrhage (ICH), with activation of a code stroke and evaluation by pediatric neurology, neurosurgery, and critical care teams. There are strong connections between these departments at all three institutions allowing for a team approach during initial diagnosis and management.

All patients with suspected ICH were evaluated, at a minimum, with a CBC with differential and PT/PTT/INR, which was followed up by further coagulopathy testing (factor deficiencies and thrombophilias) as appropriate. Vitals were obtained as part of clinical care for all patients, but the presence of hypertension was not determined in each case, as establishing hypertension in pediatric patients requires conversion to percentiles based on age, sex, and height, the latter of which is challenging to measure during acute hospitalizations. Hypertension was only noted as a possible precipitating factor when it pre-dated ICH, was considered to play a role in the acute decompensation of the child, and required treatment due to severe elevation. Otherwise, a permissive approach was used as distress and elevated ICP can both contribute to mild-moderate blood pressure elevations in this population.

Imaging was obtained for all children presenting with a concern for stroke upon arrival, with the exception of transfers requiring emergent surgical intervention and for whom neuroimaging performed at the referring center was available for review. Children typically had an initial head CT/CTA and, if stable, a brain MRI/MRA following. MRI was the first neuroimaging study in rare cases. If initial imaging revealed an obvious cerebral cavernous malformation, digital subtraction angiography (DSA) was not done. If, however, the cause of ICH remained unclear, DSA was completed as soon as possible and always within the initial hospital stay. Most children also had follow-up DSA first at 6 weeks to 3 months post-ICH if their ICH was idiopathic and then again at 1 year post-ICH. Angiography was not performed in infants (<12 months of age) in the acute period unless a vascular lesion was strongly suspected.

ICH etiology was successfully determined in all but 19% of cases with this work-up. Those whose cause was ultimately determined to be idiopathic received extensive neuroimaging with the following during their initial admission: CT (100%), MRI brain (100%), MRA brain (77%), MRV brain in 38%, and conventional angiography (90% of children ≥12 months of age & 70% overall). Further imaging (MRI/MRA/angiogram) was

completed during follow-up in 69% of cases without further clarification of etiology. Thrombophilia evaluations were undertaken in 23% and 8% of cases in the pre and post-discharge setting respectively, without notable findings. Overall, despite an extensive work-up, 19% of cases were felt to have had an idiopathic event, which consistent with what has been reported in prior studies[1].

Medical and neurosurgical interventions were at the discretion of the treating teams. Overall, hematoma evacuation occurred if the patient was not clinically stable and had a large hematoma (clinical estimate) amenable to surgical evacuation. Children were admitted to the intensive care unit (ICU) for at least 1 night for observation and transferred to the floor when clinically stable. Direct admission to the floor was considered acceptable for clinically stable children with a Glasgow coma scale of 15 when ICU beds were not available.

Physical, occupational, and speech therapists were consulted during the admission for all children with a functional deficit. They played an active role in initial inpatient rehabilitation and in discharge planning. Receipt of therapy and services was assessed at follow-up visits, but was not quantified and thus not objectively evaluated as part of this study.

Supplemental Tables and Figures

Supplemental Table I. Patient characteristics and associations (univariable and multivariable logistic regressions) with poor 2-year outcome (N=69), *p<0.05, **p<0.005.

Univariable	N (%)	OR	95% CI	p-value
Demographics				
Age, years (median, IQR)	9.7 (2.2–14)	1.0	0.9–1.1	0.7
Male	39 (57)	3.4	1.1–10	0.03*
Caucasian (reference)	45 (65)			
African-American	24 (35)	2.2	0.7–6.3	0.2
Hispanic	4 (5.8)			
Pertinent history#				
Cardiac	7 (10)	1.4	0.3–7.0	0.7
Hematologic	4 (5.8)	0.6	0.06–6.0	0.7
Rheumatologic	1 (1.4)			
Genetic	3 (4.3)	0.9	0.08–11	0.9
Clinical presentation				
Hemiparesis	36 (52)	3.7	1.0–14	0.04*
Vision deficit	6 (8.7)	0.3	0.03–2.5	0.2
Speech deficit	17 (25)	0.8	0.2–2.5	0.7
Ataxia	2 (2.9)	1.5	0.09–26	0.8
Seizure	23 (33)	1.5	0.5–4.5	0.4
Abnormal tone	10 (14)	2.2	0.6–8.6	0.3
AMS	26 (39)	13	3.9–46	<0.001**
Emesis	36 (52)	1.2	0.5–2.9	0.7
Headache	36 (52)	1.1	0.7–1.8	0.6
Hemorrhage characteristics				
Volume (% TBV)				
<2	37 (54)			
≥2	24 (35)	4.8	1.5–16	0.009**
≥4	7 (10)	17	1.9–156	0.01*
Location				
Supratentorial (reference)	63 (91)			
Infratentorial	6 (8.7)	0.9	0.2–5.4	0.9
Hemorrhage pattern				
Isolated IVH	6 (8.7)			
Isolated ICH	31 (45)			
ICH + IVH	32 (46)			
Complicating findings				
Edema	48 (70)	0.8	0.3–2.2	0.6
Hydrocephalus	24 (35)	5.4	1.7–17	0.004**
Herniation syndrome	25 (36)	7.8	2.4–25	0.001**

Etiology				
AVM	27 (39)	1.4	0.5–3.9	0.5
Idiopathic	13 (19)	0.3	0.06–1.5	0.1
Coagulopathy	12 (17)	1.1	0.3–4.1	0.9
Cavernoma	9 (13)	0.5	0.09–2.5	0.4
Aneurysm	7 (10)	5.6	1.0–31	0.05*
DVA	1 (1.4)			
Treatment and Hospital Course				
Interventions				
Mannitol/hyperosmolar saline	27 (39)			
Transfusion	13 (19)			
Hemicraniectomy	14 (20)			
Hematoma evacuation	24 (35)			
Ventriculostomy	25 (36)			
Anomaly resection/repair	28 (41)			
Length of stay (median, IQR)				
Overall	15 (9–22)	1.1	1.0–1.1	0.005*
ICU	11 (5–18)	1.1	1.0–1.2	0.002*
Multivariable		**OR**	**95% CI**	**p-value**
AMS		9.6	1.6–56	0.01*
Hemorrhage volume ≥4%		17	1.3–225	0.03*
Days in the ICU		1.2	1.0–1.3	0.006*
Age		0.9	0.8–1.1	0.3

#: Cardiac – congenital heart disease, cardiopulmonary arrest, post-infectious valvular disease; Hematologic – sickle cell disease, hemophilia B, G6PD deficiency; Rheumatologic – macrophage activating syndrome; Genetic – hereditary hemorrhagic telengiactasia

AMS: altered mental status, TBV: total brain volume, IVH: intraventricular hemorrhage, ICH: intracerebral hemorrhage, AVM: arteriovenous malformation, DVA: developmental venous anomaly, PSOM: Pediatric Stroke Outcome Measure, ICU: intensive care unit.

Supplemental Table II. Summary of cohort characteristics and univariable associations with death (N=6),*p<0.05, and **p<0.005.

	N (%)	OR	95% CI	p-value
Demographics				
Age, years (median and IQR)	11.2 (7.7–15)	1.1	0.9–1.2	0.5
Male sex	3 (50)	0.8	0.1–4.0	0.7
Race & Ethnicity				
Caucasian	4 (67)			
African American	2 (33)	0.9	0.2–5.5	0.9
Hispanic	1 (17)			
Clinical presentation				
Hemiparesis	2 (33)	0.4	0.05–2.3	0.3
Speech deficit	1 (17)	0.6	0.06–5.4	0.6
Seizure	2 (33)	1.0	0.2–5.8	1.0
Abnormal tone	1 (17)	1.1	0.1–10.7	0.9
AMS	5 (83)	9.5	1.0–87	0.05*
Emesis	3 (50)	3.4	0.9–13	0.08
Headache	2 (33)	2.0	0.9–4.2	0.08
Pertinent past medical history				
Cardiac	2 (33)	5.8	0.8–40	0.07
Hemorrhage characteristics				
Volume				
<2% TBV	2 (33)			
≥2% TBV	3 (50)	2.5	0.4–16	0.3
≥4% TBV	3 (50)	19	2.5–153	0.005**
Supratentorial	6 (100)			
Hemorrhage pattern				
Isolated IVH	1 (17)			
Isolated ICH	1 (17)			
ICH + IVH	4 (67)			
Complicating findings on imaging				
Edema	4 (67)	0.9	0.1–5.1	0.9
Hydrocephalus	4 (67)	4.2	0.7–25	0.1
Herniation syndrome	4 (67)	4.0	0.7–24	0.1
Etiology				
AVM	3 (50)	1.6	0.3–8.7	0.6
Coagulopathy	3 (50)	6.0	1.0–34	0.04*

Supplemental Table III. Comparison of studies reporting long-term outcomes (> 1 year) in non-traumatic pediatric ICH.

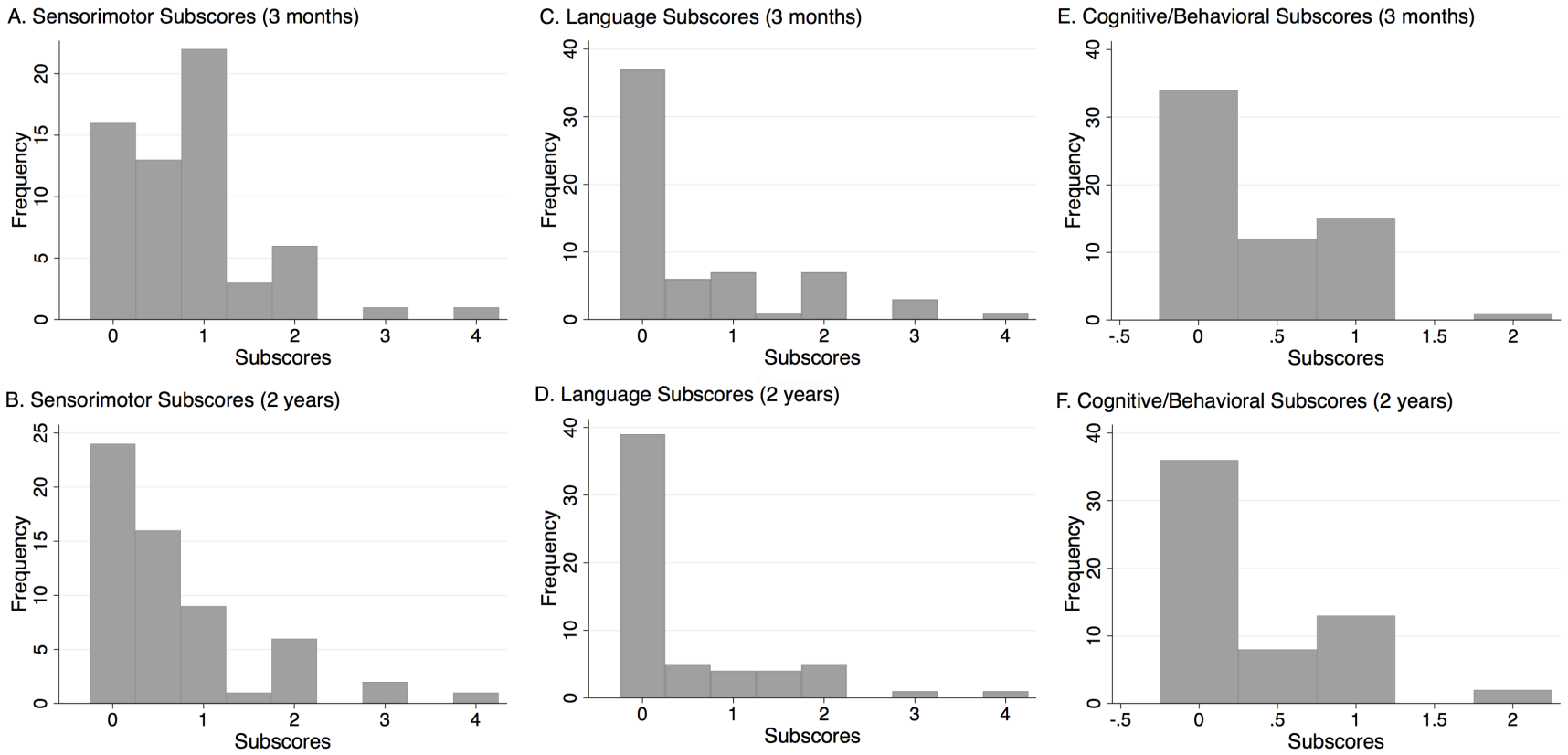
Study	N	Age range	Population	Follow-up	Outcome measures	Results
Blom[2]	31	1 mo-16 yrs	Intracranial hemorrhages (identified by ICD9 codes), including primary IVH and intracranial malignancy, excluding primary subdural or epidural hemorrhages	11 yrs (median)	- Physical exam - Neuropsychological assessment battery - Modified Rankin Scale (mRS) - Quality of life questionnaires (Short Form Health Survey, Child- and Parent-completed Child Health Questionnaires)	- Physical or cognitive impairment in 75% - No deficit in 45% (mRS 0) and no dependent patients (mRS 4-5) - Low self-esteem, behavioral, or emotional problems in majority - 36% cohort mortality rate
Meyer-Heim[3]	32	1 mo-17 yrs	Intracranial hemorrhages (identified retrospectively), including intracranial malignancy, excluding primary subdural and intraventricular hemorrhages	3 yrs (mean)	- Pediatric Clinical Scale or Glasgow Outcome Scale (based on age) -Neuropsychological assessment battery	- Good recovery in 31%, mild impairment in 22%, and severe neurological deficit in 22% - Minimal deficits in attention, memory, and behavior - 25% cohort mortality rate
Lo[4]	48*	7 d-17 yrs	Intracranial hemorrhages (identified by ICD9 codes & term search of radiology reports), including primary IVH and intracranial malignancy	25 mo (median)	- Pediatric Stroke Outcome Measure (modified for telephone)	- No deficit (PSOM 0) in 54% and poor outcome (PSOM≥5) in 10% - 34% cohort mortality rate

Lo[5]	19*	1 mo-18 yrs	Intracerebral and subarachnoid hemorrhages (identified as above), including primary IVH and intracranial malignancy, excluding isolated subarachnoid hemorrhage	5 yrs (median)	- Recovery and Recurrence Questionnaire (RRQ) - King's Outcome Scale for Childhood Head Injury (KOSCHI) - Pediatric Quality of Life Inventory - Caregiver Strain Questionnaire	- Median RRQ 1 (mild-moderate degree of impairment), with IQR 0-4 and range 0-6 - Median KOSCHI 5A (minimal impairment with daily function), with IQR 4B-5B and range 3-5B - Lower parent and patient-rated school quality of life and patient-rated physical quality of life; increased caregiver internalized stress - 34% cohort mortality rate

* Case overlap reported

ICD9 – International Classification of Diseases, Ninth Revision; IVH – Intraventricular hemorrhage

Supplemental Figure I. Distribution of domain subscores at 3-month and 2-year follow-up. A) Sensorimotor Subscores*, B) Language Subscores*, C) Cognitive/Behavioral Subscore.
*note: Left/Right Sensorimotor subscores are combined, as well as Expressive/Receptive Language subscores



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