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Predictors of Stroke Outcome in Children Admitted to Assuit University Children Hospital

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ABSTRACT

Introduction: It is possible to distinguish between ischemic and hemorrhagic strokes based on the abrupt loss of brain function they cause. Thrombotic disease is the most frequent cause of ischemic stroke, which affects children more frequently than adults, accounting for 30% to 60% of occurrences. Although less frequent in children, arteriovenous malformation is the main cause of hemorrhagic stroke.

Objectives: To detection of the rate, the possible etiology and outcome in pediatric patients with stroke "ischemic or hemorrhagic".

Patients and methods: a prospective cohort study conducted, in different Pediatric Units "the Intensive Care Unit, Intermediate Care Unit and Neurological Department", Assuit University Children Hospital from the first of January 2020 to the end of December 2021. 52 patients with stroke were included and subjected to clinical history and full examination and detailed information about stroke; type, severity, and etiology and subsequent complications: arterial ischemic stroke (AIS) or hemorrhagic stroke (HS), stroke location, and needed investigations were done.

Results: A stroke is characterised by a sudden loss of brain function brought on by a reduction in cerebral blood flow, divided into ischemic and hemorrhagic stroke. it was found that vasculopathy was the only significant predictor for stroke recurrence and also recurrence and hydrocephalus were significant predictors for death among pediatric patients with stroke.

Conclusion: There is a high mortality rate among pediatric patients with stroke; either ischemic or hemorrhagic. Establishing stroke recurrence predictors may enable more efficient therapy, which may lower the incidence of cases.

Keywords: Stroke, Vasculopathy, Arterial ischemic stroke

INTRODUCTION

A stroke is characterised by a sudden loss of brain activity brought on by a reduction in cerebral blood flow. It can happen at any stage of life, but how it manifests itself varies with age, artery involvement, and underlying risk factors. Particularly those under the age of one-year, younger children typically appear with non-specific symptoms like seizures and disturbed mental state, whereas older children typically show with focal neurologic abnormalities like hemiplegia [(1)].

Hemorrhagic and ischemic strokes in children can both occur. Ischemic stroke is characterised as localised brain tissue injury inside a vascular region brought on by a reduction in blood flow or oxygenation. In terms of processes and distribution, it is distinct from diffuse hypoxic-ischemic damage. In addition to venous infarction, which is brought on by a loss of flow in a draining cerebral vein or venous sinus, ischemic stroke, which accounts for 55% of paediatric strokes, can also be categorised as arterial ischemic stroke (AIS), which is brought on by a lack of arterial flow. Intra-parenchymal hemorrhage and spontaneous (non-traumatic) subarachnoid bleeding are both considered hemorrhagic strokes. A main venous sinus that drains the brain parenchyma is obstructed by a clot in cerebral sino-venous thrombosis (CSVT) [(2)].

Children have different risk factors for stroke than adults do. Obstructive atherosclerosis, arteriopathy, cardiovascular disease, and arrhythmias are the main risk factors in adults; same conditions are rarely risk factors in children. The two main causes of stroke in children are ischemic and hemorrhagic. The most frequent cause of ischemic stroke is thrombotic, which affects children more frequently and accounts for 30% to 60% of occurrences.

Hemorrhagic stroke, however less frequent in children, is primarily brought on by arterio-venous malformation. Studies like the International Pediatric Stroke Study (IPSS) have identified systemic risk factors for paediatric stroke, including meningitis, sepsis, and encephalitis as well as cardiac disorders, trauma, and sickle cell disease. However, in the majority of cases, no systemic disease was discovered [(3)].

The main aim of the study was the detection of the rate, the possible etiology and outcome in pediatric patients with stroke "ischemic or hemorrhagic".

PATIENTS AND METHODS

This study was a prospective cohort study conducted, in different Pediatric Units "the Intensive Care Unit, Intermediate Care Unit and Neurological Department", Assuit University Children Hospital from the first of January 2020 to the end of December 2021. 52 patients with stroke were included.

Inclusion criteria: Gender: boys and girls, age: from 1 month up to 18 years, patients who were diagnosed as stroke (hemorrhagic or ischemic) by CT or MRI and acceptance of caregivers to participate in the study.

Exclusion criteria: Neonates (less than one month), stroke caused by trauma, children or parents who refused to participate in this study.

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Methodology:

Eligible children were subjected to the following preliminary evaluation: Personal data: Name, age, sex, family history, address, socioeconomic status and any risk factor or possible related underlying diseases for stroke.

Detailed clinical examination included: Vital sign: Blood pressure, heart rate, temperature and respiratory rate. Systematic examination: Chest examination, cardiac examination, abdominal examination and neurological examination. Medical details about the nature, seriousness, and causation of strokes. Following complications include: AIS or HS; stroke location (i.e., hemispheric/supra-tentorial versus posterior fossa, as determined by CT scan and/or MRI reports); initial coma presence (yes/no); Glasgow Coma Scale score (GCS), when available (N = 46); and occurrence of seizures requiring continued treatment after the acute phase (excluding isolated initial seizures without prolonged treatment).

The following motor and sensory deficits, the existence of cerebellar symptoms, and discharge from the rehabilitation department were all assessed neurologically and functionally during the course of a medical examination performed at admission and at discharge (ataxia and coordination disorders, visual field defect). Investigations: CT, MRI, MRA, MRV, CBC, liver function, echo, protein s/c function and hemoglobin electrophoresis.

Ethical Approval:

Each caregiver of every study participant provided written informed permission after the South Valley University Ethics Board approved the study. The Declaration of Helsinki, the World Medical Association's code of ethics for studies involving humans, guided the conduct of this work.

Data Analysis

SPSS (statistical package for the social sciences; SPSS Inc., Chicago, IL, USA) version 22 was used for all statistical calculations. Mean, standard deviation, median, and range were used to describe quantitative data. Qualitative data were expressed as frequencies and percentages. The Mann Whitney U test was used to compare quantitative variables. When comparing categorical data, the Chi square test was used. The Fischer test was used in its place when the expected frequency was less than 5.

Odds ratios (OR) with 95% Confidence Intervals (CI) and logistic regression were computed to find pertinent factors related to recurrence and death. Significant results are those with a two-tailed P value of 0.05 or less.

RESULTS

The final diagnosis of the studied patients is shown in table 1.

Table 1: Final diagnosis of the studied participants (n=52)

Variable name		N	(%)
Type of stroke	Infarction	28	(53.8)
	Hemorrhagic	24	(46.2)
Laterality of infarction	Unilateral	19	(67.9)
	Bilateral	9	(32.1)
Site of hemorrhagic stroke	Intra-cerebral	9	(37.5)
	Intra-ventricular	4	(16.7)
	Subdural	7	(29.2)
	Subarachnoid	4	(16.7)
MRA	Normal	31	(59.6)
	Abnormal finding	7	(13.5)
	Not done	14	(26.9)
MRV	Normal	30	(57.7)
	Abnormal finding	8	(15.4)
	Not done	14	(26.9)
Recurrence	No	43	(82.7)
	Yes	9	(17.3)
Death	No	35	(67.3)
	Yes	17	(32.7)

Data are presented as number (percentage). MRA: Magnetic Resonance Angiography, MRV: Magnetic Resonance Venography.

Younger aged children were more liable to develop hemorrhagic stroke. Also, children with coagulation diso rders were more liable to develop hemorrhagic stroke (Table 2).

Table 2: Difference in the demographic and clinical variables of the studied participants according to the type of stroke (n=52)

Variable name	Type of stroke		P value
	Infarction (n=28)	Hemorrhagic (n=24)	
Sex			0.143
▪ Male	13 (46.4)	16 (66.7)	
▪ Female	15 (53.6)	8 (33.3)	
Age (years)			
▪ Mean ± SD	6.02±5.79	3.37±4.93	**0.010***
▪ Median (range)	4 (1 month – 16 years)	3 (1 month – 13 years)	
Family history			
▪ Negative	28 (100)	23 (95.8)	0.462
▪ Positive	0 (0)	1 (4.1)	
Socioeconomic Status			0.571
● High	9 (32.1)	6 (25.0)	
● Poor	19 (67.9)	18 (75.0)	
Complaint			0.094
● Focal	9 (32.1)	3 (12.5)	
● Generalized	19 (67.9)	21 (87.5)	
Risk factors			
● Cardiac	4 (14.3)	1 (4.2)	0.358
● Infection	8 (28.6)	5 (20.8)	0.521
● Vasculopathy	5 (17.9)	1 (4.2)	0.199
● Thrombophilia	6 (21.4)	2 (8.3)	0.262
● Renal failure and Hypertension	6 (21.4)	3 (12.5)	0.480
● Coagulation disorder	0 (0.0)	5 (20.8)	**0.016***
● Aplastic anemia	0 (0.0)	1 (4.2)	0.462
● Brain trauma	1 (3.6)	1 (4.2)	1
● Scorpion stings	1 (3.6)	0 (0.0)	1

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage).
*: Significant

Children with hemorrhagic stroke were presented with “pallor”. Meanwhile children with ischemic stroke were presented with fever (Table 3).

Table 3: Difference in the systematic examinations of the studied participants according to the type of stroke (n=52)

Variable name		Type of stroke				*P value*
		Infarction (n=28)		Hemorrhagic (n=24)		
Vital signs						
▪ **Blood pressure**	Normotensive	13	(46.4)	10	(41.7)	0.543
	Hypotensive	9	(32.1)	11	(45.8)	
	Hypertensive	6	(21.4)	3	(12.5)	
▪ **Heart rate**	Normal	15	(53.6)	12	(50.0)	0.797
	Tachycardia	13	(46.4)	12	(50.0)	
▪ **Temperature**	Normal	5	(17.9)	16	(72.7)	**0.000***
	Feverish	23	(82.1)	6	(27.3)	
▪ **Respiratory rate**	Normal	10	(35.7)	10	(41.7)	0.602
	Tachypnea	17	(60.7)	12	(50.0)	
	Bradypnea	1	(3.6)	2	(8.3)	
▪ **Pallor**	No	17	(60.7)	2	(8.3)	**0.000***
	Yes	11	(39.3)	22	(91.7)	
▪ **Jaundice**	No	28	(100.0)	22	(91.7)	0.208
	Yes	0	(0.0)	2	(8.3)	
▪ **Cyanosis**	No	26	(92.9)	20	(83.3)	0.397
	Yes	2	(7.1)	4	(16.7)	
▪ **Edema**	No	24	(85.7)	22	(91.7)	0.674
	Yes	4	(14.3)	2	(8.3)	
General examination						
▪ **Tachypnea**	No	11	(39.3)	13	(54.2)	0.283
	Yes	17	(60.7)	11	(45.8)	
▪ **Tachycardia**	No	14	(50.0)	12	(50.0)	1
	Yes	14	(50.0)	12	(50.0)	
▪ **Hepatomegaly**	No	23	(82.1)	19	(79.2)	1
	Yes	5	(17.9)	5	(20.8)	
▪ **Peripheral edema**	No	24	(85.7)	21	(87.5)	1
	Yes	4	(14.3)	3	(12.5)	
▪ **Valve lesion or cardiac operation**	No	25	(89.3)	23	(95.8)	0.615
	Yes	3	(10.7)	1	(4.2)	
▪ **Ascites**	No	28	(100.0)	24	(100.0)	----
	Yes	0	(0.0)	0	(0.0)	
▪ **Organomegally**	No	23	(82.1)	19	(79.2)	1
	Yes	5	(17.9)	5	(20.8)	
▪ **Headache**	No	13	(46.4)	16	(66.7)	0.143
	Yes	15	(53.6)	8	(33.3)	
▪ **Vomiting**	No	5	(17.9)	5	(20.8)	1
	Yes	23	(82.1)	19	(79.2)	
▪ **Gait limbic ataxic**	Normal	12	(48.0)	7	(53.8)	0.732
	Abnormal	13	(52.0)	6	(46.2)	
▪ **Conscious level GCS**	Normal	7	(25.0)	3	(12.5)	0.262
	DCL	19	(67.9)	21	(87.5)	
	Drowsy	2	(7.1)	0	(0.0)	
▪ **Occurrence of seizures**	No	1	(3.6)	2	(8.3)	0.590
	Yes	27	(96.4)	22	(91.7)	
▪ **Tone**	Average	0	(0.0)	1	(4.2)	0.199
	Hypertonia	23	(82.1)	22	(91.7)	
	Hypotonia	5	(17.9)	1	(4.2)	
▪ **Reflexes**	Average	0	(0.0)	1	(4.2)	0.261
	Hyperreflexia	24	(85.7)	22	(91.7)	
	Hyporeflexia	4	(14.3)	1	(4.2)	
▪ **Visual field defect**	No	25	(89.3)	20	(83.3)	0.690
	Yes	3	(10.7)	4	(16.7)	

Data are presented as number (percentage).

Children with ischemic stroke were more likely to develop weakness or paralysis as compared to children suffered from hemorrhagic stroke (15 (53.6%) versus 6 (25.0%), P=0.036). Meanwhile; children with hemorrhagic stroke mainly developed hydrocephalus as compared to children suffered from ischemic stroke (3 (10.7%) versus 9 (37.5%), P<0.05). Other factors show no difference according to the type of stroke (Figure 1).

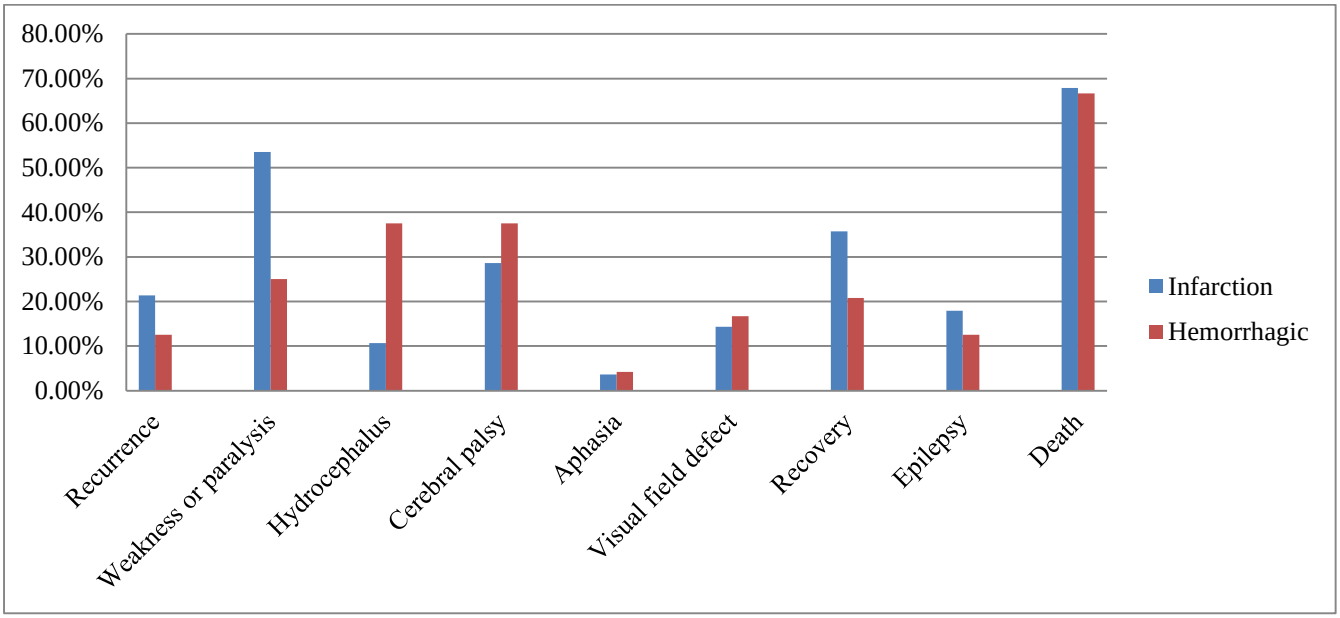

Figure (1) outcome of the studied patients

On univariate and multivariate analysis, we found that vasculopathy was the only significant predictor for stroke recurrence, vasculopathy cause 16 times increase in the risk of stroke recurrence (Table 4).

Table 4: Predictors of stroke recurrence

Variables	N	Univariate analysis			Multivariate analysis		
		OR	**P value**	**95% CI**	**OR**	**P value**	**95% CI**
Gender							
Male	29	ref			ref		
Female	23	5.906	**0.039***	1.091 – 31.969	3.845	0.145	0.627 – 23.561
Vasculopathy							
No	46	ref			ref		
Yes	6	16.40	**0.005***	2.369 – 113.521	16.40	**0.005***	2.369 – 113.521
Renal failure and hypertension							
No	43	ref			ref		
Yes	9	6.080	**0.028***	1.213 – 30.473	3.895	0.172	0.553 – 27.443
Site of hemorrhage						Not included in the final model	
Intra-cerebral	9	ref					
Intra-ventricular	4	1	1	0.000 - NA			
Subdural	7	1	0.999	0.000 - NA			
Subarachnoid	4	1	1	0.000 - NA			

OR: Odds ratio, CI: confidence interval, NA: not achieved, *: Significant

On univariate and multivariate analysis; recurrence and hydrocephalus were significant predictors for death among pediatric patients with stroke. As pediatric patients who developed stroke recurrence are ten times more likely to die, and pediatric patients who developed hydrocephalus were about seven times more likely to die (Table 5).

Table 5: Predictors of stroke associated deaths

Variables	N	Univariate analysis			Multivariate analysis		
		OR	**P value**	**95% CI**	**OR**	**P value**	**95% CI**
Recurrence							
● **No**	43	ref			ref		
● **Yes**	9	5.818	**0.026***	1.240 – 27.302	9.561	**0.009***	1.774 – 51.546
Hydrocephalus							
● **No**	40	ref			ref		
● **Yes**	12	4.200	**0.038***	1.086 – 16.242	6.794	**0.012***	1.521 – 30.351
Visual field defect							
● **No**	44	ref			ref		
● **Yes**	8	4.444	0.064	0.918 – 21.527	2.897	0.252	0.470 – 17.862

OR: Odds ratio, CI: confidence interval, *: Significant

DISCUSSION

Ischemic and hemorrhagic strokes are equally possible. Although venous obstruction of cerebral veins or sinuses can also cause ischemic stroke, arterial occlusion is more usually the cause. A cerebral artery rupture or bleeding into the site of an acute ischemic stroke are both causes of hemorrhagic stroke (AIS) [(4)]. In our study we found that, 53.8% were suffering from ischemic stroke and 46.2% were hemorrhagic stroke.

In our study by comparing the demographic and clinical variables of the studied participants according to the type of stroke we found that hemorrhagic stroke was significantly occurring in younger aged children, and in children who suffered from coagulation disorder. Also, we found that children with hemorrhagic stroke were presented with anemia "pallor", and mainly developed hydrocephalus as compared to children suffered from ischemic stroke.

Chiang and Cheng [(5)] reported that one of the main causes of ischemic stroke was moyamoya illness. Ischemic stroke was caused by thalassemia, autoimmune illness, aneurysms, and renal diseases. AVM (4.7%) and other cerebral vascular abnormalities (17.9%), CNS neoplasms, hematological malignancy, idiopathic thrombocytopenia, and abusive brain trauma were all significantly more common causes of hemorrhagic stroke.

For ischemic stroke; we found that children who were suffering from ischemic stroke were significantly presented with high temperature (P<0.001) and mainly developed weakness or paralysis as compared to children with hemorrhagic stroke (P=0.036). Also, we found that children who were suffering from cardiac risk factors, vasculopathy or thrombophilia were more likely to develop ischemic stroke; yet not reach statistically significant result. In line with our study **Felling *et al.*** [(6)] reported that thrombophilia, as a risk factor for stroke in children, can occur simultaneously in those children with cardiac risk factors. Furthermore, **Sinclair *et al.*** [(7)] stated that for children with both cardiac and thrombotic risk factors, the incidence of ischemic stroke was 12- fold.

The frequency of stroke recurrence in paediatric populations varies depending on the type and quantity of stroke risk factors identified in the child [(8)]. In the current investigation, we discovered that 17.3% of the children were experiencing recurrent ischemia events. The follow-up period's length, which varies widely between research, is one of the main challenges to accurately estimating the frequency of recurrent stroke.

In the present study we found that children who were suffered from vasculopathy or renal failure and hypertension, and those with subdural hemorrhagic stroke were more likely to develop recurrent ischemic attacks. Also, on univariate and multivariate analysis we found that vasculopathy was the only significant predictor for stroke recurrence, vasculopathy cause 16 times increase in the risk of stroke recurrence.

This finding is corroborated by a recent study, which found that the presence of vasculopathy, particularly moyamoya disease and focal cerebral arteriopathy of childhood (FCA), which increases the risk of recurrent stroke by five times, is one of the confirmed risk factors for recurrent stroke in children.[(9)].

On the other hand other studies reported other risk factors for the development of recurrence among pediatric patients. Low socioeconomic level, recent illnesses, and insufficient immunisation are all risk factors for recurrent AIS in children[(10)].

In the current study it was found that those children who were presented with generalized complaints (including alteration of conscious level with or without seizures), and those children who developed recurrence and/or hydrocephalus were more likely to die. Also, on univariate and multivariate analysis we found that recurrence and hydrocephalus were significant predictors for death among pediatric patients with stroke. As we found that pediatric patients who developed stroke recurrence are ten times more likely to die, and pediatric patients who developed hydrocephalus are about seven times more likely to die.

In concordance with our results, **Aarnio *et al.*** [(11)] discovered that stroke patients who experienced a second stroke had an abnormally high mortality rate. The most significant risk factor for death in the patient

group under study after a first AIS was stroke recurrence, with a hazard ratio (HR) of 16.68. Additionally, in accordance with our study, another author claimed that recurrent stroke was seen to raise the risk of patients' mortality, and the same author also reported a relationship between survival probability and the economic status of the patient's country. Children who die from strokes in developing countries 30 to 60 times more frequently than in developed countries. [(12)].

Lopez-Espejo *et al*. documented that the location of the circulation infarcts is related not only to stroke symptoms, but also to outcomes in children. Anterior plus posterior stroke in children is a risk factor for death (HR = 2.43, 95% CI 1.42–4.61, p = 0.026) [(13)].

Brush *et al*.[(14)] stated that the presence of hypertension within 72 hours after stroke occurrence is a risk factor for death, with a risk ratio of 4.5. The number of days the patient had hypertension in the acute phase is also correlated with stroke mortality (p = 0.043).

CONCLUSION

Recognizing the causes of stroke and, in certain situations, preventing disease may be made possible by knowing the risk factors for stroke recurrence in children. There is little doubt that a number of risk factors, such as vasculopathy, influence the cause of a stroke as well as the presence of its aftereffects, such as recurrence. Establishing stroke recurrence predictors may enable more efficient therapy, which may lower the incidence of cases. Pediatric patients who developed recurrence and those who were suffered from hydrocephalus have increased risk of mortality.

RECOMMENDATION

Policy frameworks must be constructed that include short-, medium-, and long-term solutions to this problem in order to lower the incidence of childhood stroke in our neighbourhood. Once stroke is considered, further examination, initiation of imaging, and institution of supportive therapy should proceed concurrently. The Pediatric National Institutes of Health Stroke Scale (PedNIHSS) is an 11-item scale to assess the severity of stroke. It has been validated for use in children and infants and is available online for free (http://stroke.ahajournals. Org / content / 42/ 3/ 613/ suppl/ DC1). Rapid identification and differentiation of ischemic and hemorrhagic stroke, is very important, for substantially proper treatments.

DECLARATIONS

- **Consent for Publication:** I confirm that all authors accept the manuscript for submission
- **Availability of data and material:** Available
- **Competing interests:** None
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- **Conflicts of Interest:** Regarding the publication of this paper, the authors declare that they have no conflicts of interest.

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