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Original article

Risk factors and motor outcome of paediatric stroke patients

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Abstract

Background: Childhood stroke causes significant morbidity and mortality. In this study, we aimed to define the presenting findings, causes, risk factors and motor outcomes of our patients.

Methods: We retrospectively analysed patients aged from 1 month to 18 years who were diagnosed as having the first onset of stroke between January 2006 and December 2015. Presenting features, causes, risk factors, recurrence rate and motor outcomes were recorded. Motor outcome was evaluated by the gross motor function classification system.

Results: Forty-seven children were included in the study. Thirty-eight (78.7%) children had an arterial stroke, 9 (19.1%) had a venous stroke. The median age at the time of presentation was 60 months (3–214). Thirty-two patients (68%) presented with a focal neurological sign and 9 presented with seizure (19.1%). Patients who had a venous stroke presented with more diffuse neurological symptoms than those who had an arterial stroke. At least one risk factor for stroke was identified in 74.5% of the patients; the most common causative factor was prothrombotic state seen in 16 patients (33.5%). Stroke recurred in 5 patients (10.6%); coexistence of multiple factors was a risk factor for recurrence. Presenting with seizure was not a facilitator for epilepsy. Thirty-two (68%) patients had a favourable motor outcome. Younger age (24 months versus 114 months) and presenting with focal neurological signs were related to non-favourable motor outcome.

Conclusion: Our cohort demonstrates that most of the children had a risk factor for stroke and have had favourable motor outcome. However, younger age and presenting with focal seizures are related to non-favourable motor outcome.

Keywords: Childhood epilepsy; Cause; Outcome; Risk factors; Recurrence; Stroke

1. Introduction

Increasing attention is being paid to childhood stroke worldwide. Stroke is as common as brain tumours in children, with an estimated incidence of 2.1–13.0 per 100,000 children per year [1]. Causes of childhood stroke differ significantly from those of typical adult stroke and are grouped as: (1) arteriopathy, (2) cardiac disorders, (3) chronic and systemic disorders, (4) prothrombotic states, (5) acute head and neck disorders, (6) chronic head and neck disorders, and (7) undetermined [2].

The outcome of stroke in children is considered to be more favourable than in adults, because children have better brain plasticity. However, several studies have reported that survivors of childhood stroke have long-term physical disabilities and cognitive impairment [3]. In this study, we evaluated the causes, presenting clinical

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findings, recurrence rates and motor outcomes of our stroke patients.

2. Materials and methods

We retrospectively identified all children aged between 1 month and 18 years who were diagnosed as having initial onset of arterial or venous stroke between January 2006 and December 2015 in Ankara Paediatric Hematology Oncology Research and Training Hospital (Ankara, Turkey), a tertiary hospital. Cases were identified using the International Classification of Diseases (ICD) codes for stroke and medical records were reviewed retrospectively. Stroke was defined as an acute neurological deficit lasting >24 h caused by ischaemia with or without haemorrhagic damage to the brain as shown on neuroimaging scans (cranial magnetic resonance imaging with or without magnetic resonance angiography, magnetic resonance venography). These scans show parenchymal infarcts in an arterial territory corresponding to the clinical symptoms. Fifty children were included in the study. Three patients who died in the acute stroke period and patients with suspected perinatal stroke (especially patients <6 months old with an infarct area) were excluded from the study. We used the International Paediatric Stroke Surveillance risk factors for childhood stroke to classify the patients. First-line investigations on admission included complete blood count, blood glucose, serum electrolytes, blood urea nitrogen, creatinine, coagulation, liver function tests, sedimentation, triglycerides, total cholesterol, C-reactive protein, serum iron level, serum iron-binding capacity, serum ferritin level, metabolic screening, electrocardiography, and echocardiography. Additional investigations included hematology, protein C, protein S, fibrinogen level, anti-thrombin III level, factor VIII, factor IX, activated protein C resistance, prothrombin time, activated thromboplastin time, anti-cardiolipin factors, homocysteine levels; and for genetic investigations, factor V Leiden, factor II G20210A, and methyl tetrahydrofolate reductase (MTHFR) C 677 T were conducted. Because heterozygous mutations are very common in the population, only MTHFR homozygous mutation was considered as a prothrombotic risk factor. The coexistence of multiple factors (more than one risk factor) was also evaluated. Outcomes were noted only for motor disability according to clinical status at least 2 years after the first admission. Motor disability was measured using the gross motor function classification system (GMFCS). A GMFCS score of 0–1 was noted as a favourable motor outcome, whereas a score of 2–5 was noted as a non-favourable motor outcome. We defined epilepsy as a seizure after discharge and treatment with anticonvulsants 6 months after the occurrence of stroke.

2.1. Statistical analysis

Statistical analysis was performed on a personal computer using SPSS/PC version 15.0. Differences in proportions were assessed by the χ^2 test or the Fisher exact test, as appropriate. The Mann-Whitney U test and the Student t test were used for analysis of data between the groups. The cut-off for statistical significance was set at $P < 0.05$.

3. Results

A total of 47 children were included in the study; 25 were girls (53.2%) and 22 were boys (46.8%). Thirty-eight children (78.7%) had an arterial stroke including 3 with haemorrhagic stroke and 9 (19.1%) had a venous stroke (cerebral venous sinus thrombosis) including 3 with haemorrhagic stroke. The median age at the time of presentation was 60 months (3–214). The median age of those who had a venous stroke was 156 months (10–192) and 42 months (3–214) for those who had an arterial stroke; patients who had a venous stroke were significantly older ($P = 0.042$). Thirty-two patients (68%) presented with a focal neurological sign, especially hemiparesis and/or cranial nerve involvement (Table 1). Patients who had a venous stroke (7 of 9) presented with more diffuse neurological signs than those who had an arterial stroke (8 of 38) patients ($P = 0.001$). Seizures occurred in 9 patients (19.1%) (Fig. 1), 7 occurring in the first 24 h, 3 with status epilepticus, 2 with generalized tonic-clonic seizures and 4 with focal seizures. Three patients who had a venous stroke and 6 who had an arterial presented with seizure at first hospitalization. Epilepsy developed in 9 patients; seizure was the presenting symptom in 3 of these patients. All had an arterial stroke, but this was not significant ($P = 0.104$). Presenting with seizure or status epilepticus was not a facilitator for epilepsy ($P = 0.066$) and only one patient (11.1%) had refractory epilepsy. We identified at least one risk factor for stroke in 36 patients (74.5%) and the most common causative factor was prothrombotic state seen in 16 patients (33.5%) (Table 1). The distribution of the patients with prothrombotic state is presented in Table 2. Prothrombotic state was the most common causative factor for arterial stroke; acute head and neck disorders were the most common factor in patients who had a venous stroke. Coexistence of multiple factors was detected in 11 patients (23.4%).

Stroke recurred in 5 patients. The risk factors for these patients were determined as cardiac disorders in 2 patients, arteriopathy (Takayasu arthritis) in 1 patient, chronic and systemic disorders and treatments (nephrotic syndrome) in 1 patient and undetermined factors in 1 patient. The coexistence of multiple factors was a risk factor for recurrence ($P = 0.002$). Median

Table 1
Demographic and clinical findings of the patients.

	n (%)
Age (months), median (min–max)	60 (3–214)
Sex	
Female	25 (53.2)
Male	22 (46.8)
Risk factor	
Prothrombotic states	16 (33.5)
Acute head and neck disorders	7 (15.5)
Cardiac disorders	6 (12.8)
Chronic and systemic disorders and treatments	4 (8.5)
Arteriopathy	2 (4.3)
Chronic head and neck disorders	1 (2.1)
Undetermined	11 (23.3)
Coexistence of multiple risk factors	11 (23.4)
Diffuse neurological signs (alteration of consciousness, headache, nausea and/or vomiting, seizure)	15 (32)
Focal neurological signs (hemiparesis/plegia, cranial nerve palsy, visual-speech impairment, nystagmus)	32 (68)
Hemisphere affected in arterial stroke	38 (1 0 0)
Left	18 (47.4)
Right	14 (36.8)
Both	6 (15.8)
Treatment	
Low molecular weight heparin	19 (40.4)
Aspirin	11 (23.5)
Coumadin	2 (4.3)
Recurrence	5 (10.6)

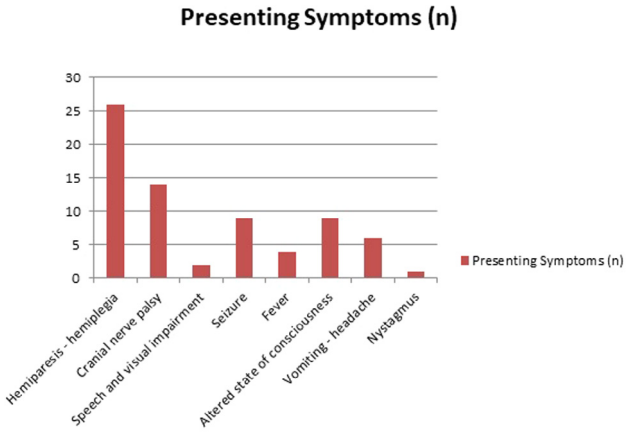

Fig. 1. Presenting symptoms of the patients.

Table 2
Prothrombotic states.

Prothrombotic state	No. of patients (N = 16)
Elevated lipoprotein(a)	4
Factor V Leiden mutation	4
Increased homocysteine	1
Antithrombin III deficiency	1
Protein S deficiency	1
MTHFR polymorphism[a]	3
Anticardiolipin-IgG/-IgM	1
Increased homocysteine + MTHFR polymorphism	1

[a] MTHFR polymorphism: homozygous mutation C677T.

follow-up time for all patients was 4 years (24–180 months).

The motor outcomes of the patients in terms of GMFCS are listed in Table 3. Thirty-two patients (68%) had a favourable motor outcome. Favourable motor outcome was related to older age ($P = 0.018$) and venous stroke ($P = 0.022$), but it was not related to sex ($P = 0.989$), coexistence of multiple risk factors ($P = 0.706$) or recurrence ($P = 0.545$) (Table 4). Younger age (24 months versus 114 months) was related to non-favourable outcome.

4. Discussion

Childhood stroke is a life-threatening condition and results in persistent motor deficits in most survivors; epilepsy, cognitive or behavioural abnormalities commonly occur [4,5]. We retrospectively evaluated 47 patients

Table 3
Motor outcome in stroke survivors.

Motor outcome (GMFCS)	n (%)
0 (F)	23 (49)
1 (F)	9 (19)
2 (NF)	12 (25.5)
3 (NF)	2 (4.5)
4 (NF)	1 (2)
5 (NF)	0

F, favourable motor outcome; NF, non-favourable motor outcome.

Table 4
Characteristics of patients with favourable and non-favourable motor outcome.

	Favourable, n (%)	Non-favourable, n (%)	*P* value
Overall	32 (68)	15 (32)	
Sex			
Female	17 (53.1)	8 (53.3)	0.989
Male	15 (46.8)	7 (46.6)	
Age (months), median (min–max)	114 (4–198)	24 (3–214)	0.018
Risk factor (±)	25/32 (78.1)	11/15 (73.3)	0.718
Coexistence of multiple factors	8/32 (25)	3/15 (20)	0.706
Diffuse neurological signs	12/32 (37.5)	3/15 (20)	0.230
Focal neurological signs	20/32 (62.5)	12/15 (80)	0.230
Recurrence	4/32 (12.5)	1/15 (6.66)	0.545
Arterial/venous			
Arterial	23 (71.8)	15 (1 0 0)	0.022
Venous	9 (28.0)	0	
Follow-up time (months), median (min–max)	41 (24–180)	72 (24–120)	0.67

who had childhood stroke in terms of causes, recurrence rates and motor outcomes. We found that patients who had a venous stroke were slightly older and diffuse neurological symptoms were more frequent. The most common cause for stroke in our study group was prothrombotic state detected in 16 patients (33.5%). The reported prevalence of inherited prothrombotic states in patients with ischaemic stroke is highly variable, ranging from 0% to 63% [6]. The most causative risk factor for stroke varies among studies. A study from Turkey by Per et al. [7] reported that the most common risk factor was infection; it was found to be arteriopathy in a study conducted in China [8]. Improvements in tests for prothrombotic state have made it possible to identify these causes. Among the many risk factors reported, the cause remained undetermined in almost one-third of the patients [2].

Some patients had multiple cofactors. Lengthier et al. [9] reported that multiple cofactors predict poor outcome and recurrence. The risk of recurrence of childhood stroke is reported in the literature to be between 7% and 41% and recurrence rates correlated with the causes, mostly with cardiac disease, Moya Moya disease, and genetic thrombophilia [7,9,10]. In our study, 5 patients (10.6%) experienced recurrent stroke, 4 of whom had at least one risk factor. Moreover, patients with more than one risk factor had higher recurrence rates, but this was not related to non-favourable motor outcome.

Children with an acute seizure at the time of stroke or within 24 h after admission were more vulnerable to epilepsy than the children who did not have a seizure at the time of the stroke [11,12]. In our study group, the occurrence of epilepsy was significantly higher in patients presenting with seizure, but it was not statistically significant. Seizures occurred in the first 24 h in 7 of 9 patients. In the Copenhagen Stroke Study, younger age was associated with post-stroke epilepsy, whereas the Askershus Stroke Study found no association [13,14]. The results of our study were similar to those from the Copenhagen Stroke Study. Furthermore, we did not find any relationship between the cause of stroke and post-stroke epilepsy. Non-convulsive status is reported in 3.6% of 889 adult patients in a study where prolonged video EEG was performed in all acute ischemic stroke patients. In 40.6% of patients with non-convulsive status epilepticus no clinical suspect was present. In our study we repeated routine interictal EEG for patients with encephalopathy or recurrent seizures, but we did not performed prolonged EEG monitoring, so we might underdiagnose patients with non-convulsive status epilepticus [15].

Most studies on childhood stroke have revealed that neurological deficits occurred in 50%–85% of survivors [16,17]. In our study, 68% of our patients had a favourable motor outcome by the GMFCS with a median follow-up of 4 years. Simonetti et al. [18] reported functional outcome using a modified Rankin Scale score; 56% of children and 55% of young adults had a good functional outcome after a median follow-up duration of 6.9 years. Although the long-term outcome in children after acquired brain disease is considered better than in adults because of the increased plasticity of the immature brain, Simonetti et al. [18] compared long-term clinical outcomes of stroke in patients aged <16 years and in young adult patients (16–44 years) and found no major differences in long-term functional outcomes in terms of mortality or disability, and recurrence rates. Other studies have suggested that serious residual neurological impairment occurs after early insult, with significant deficits in infancy described by Anderson et al. [19,20]. In our study, we also found out that younger age led to non-favourable motor outcome.

4.1. Limitations

Because this study was conducted retrospectively, psychosocial aspects and behavioural outcomes were not analysed. Thus, the Paediatric NIH Stroke Scale was not used. Screening patients retrospectively by ICD codes could lead to missing and loss of data.

5. Conclusion

In our study, patients who had a venous stroke presented with more diffuse neurological symptoms than those who had an arterial stroke, and seizures were mostly seen within the first 24 h after admission, although this was not a facilitator for post-stroke

epilepsy. Coexistence of multifactorial diseases leads to recurrence of stroke. Most children had a favourable motor outcome, which was related to older age and venous stroke.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.braindev.2018.07.004.

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