Evaluation of 39 children with stroke regarding etiologic risk factors and treatment

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SUMMARY: Hergüner MÖ, İncecik F, Elkay M, Altunbaşak Ş, Baytok V. Evaluation of 39 children with stroke regarding etiologic risk factors and treatment. Turk J Pediatr 2005; 47: 116-119.

Stroke etiologies in childhood differ from those in adulthood. While in children, congenital and acquired heart diseases and sickle cell anemia (SCA) are commonly seen causes, atherosclerosis is the main cause in adults. In this study, 39 children admitted to our hospital with ischemic stroke were evaluated according to etiologic factors and treatment regimens with comparison to the literature. Congenital-acquired heart disease and central nervous system infections (meningoencephalitis) were the most common causes in our series. Only one patient had dual pathology. As a result, cardiologic and infectious causes appeared to be the most important etiologic factors, especially in our region. Furthermore, etiologic factors rather than treatment used may play an important role in stroke recurrence.

Key words: stroke, risk factors, treatment.

Recently, pediatric stoke has been recognized in children more often than in previous years. Broderick et al.¹ found an overall incidence of 2.7 cases/100,000/year and a 44 to 61% ratio of ischemic stroke, similar to the results of Schoenberg et al.².

Stroke etiologies in childhood differ from those in adulthood. While in children, congenital and acquired heart diseases and sickle cell anemia (SCA) are commonly seen causes, atherosclerosis is the main cause in adults. The other etiologic factors determined in childhood are infections, vascular anomalies, collagen tissue diseases, congenital/acquired coagulation disorders, and prothrombotic abnormalities (anticardiolipin antibodies, lupus anticoagulant, and deficiencies of protein C, S, antithrombin, and plasminogen). Recently, abnormal activated protein C resistance (factor V Leiden), factor II G20219A variant, and methylenetetrahydrofolate reductase thermolabile variant (MTHFR C677T) have been reported³⁻⁵. As the number of risk factors increases, the risk of stroke increases. However, in approximately 10 to 33% of children with stoke, the etiology may not be determined.

In this study, 309 children admitted to our hospital with arterial ischemic stroke were evaluated according to etiologic factors and treatment regimens by comparison with the literature.

Material and Methods

Thirty-nine patients who were admitted to the Department of Pediatric Neurology between 1997 and 2003 and diagnosed as arterial ischemic stroke clinically and radiologically were enrolled in this study. Patients with transient ischemic attacks and neonatal stroke were excluded. Age at stroke, sex, past medical history, family history, clinical findings at admission, history of seizure, and radiological findings were recorded.

Cerebral computerized tomography (CT) and/ or magnetic resonance imaging (MRI) in all patients and magnetic resonance angiography (MRA) in five patients were performed.

Complete blood count, sedimentation rate, liver function tests, BUN, creatinine, electrolytes, serum iron level, serum iron binding capacity, serum ferritin level, total cholesterol, triglycerides, lipoprotein (a), VDRL, chest Xray, electrocardiogram and echocardiography were done in all patients. To rule out specific etiologic factors, serologic tests, immunologic profile, cerebrospinal fluid (CSF) lactate and pyruvate, and hemoglobin electrophoresis were investigated.

Prothrombin time, activated thromboplastin time, fibrinogen, protein C and S activity, antithrombin III level, total plasma homocysteine level, lupus anticoagulant, and anticardiolipin levels were examined to exclude causes of thrombophilia. If an abnormal result was detected in the acute period, it was repeated three months later.

Additionally, factor V Leiden mutation, factor II G 20210A variant, and MTHFR variant were studied in all patients.

Results

The age range of the 39 patients was between 1 month and 14 years (mean: 54.94 ± 51.40 months). The male/female ratio was 19/20.

All patients except two had one stroke attack. One of these two patients with recurrent strokes had idiopathic hypertrophic cardiomyopathy associated with protein S deficiency, and the other had nephritic syndrome. Etiologic factors of the patients are shown in Table I. Congenital-acquired heart disease and central nervous system (CNS) infections (meningoencephalitis) were the most common cause. Only one patient had dual pathology (hypertrophic cardiomyopathy and protein S deficiency).

Table I. Etiologic Risk Factors in Stroke Patients

Etiologic risk factor	n	%
Cardiac diseases	9	23
Infectious diseases	6	15.3
Sickle cell anemia	4	10.2
MTHFR*	4	10.2
Trauma	3	7.7
Dehydration	2	5.1
Factor V Leiden mutation	1	2.5
Protein C deficiency	1	2.5
Nephrotic syndrome	1	2.5
AT III* deficiency	1	2.5
Anoxia	1	2.5
HCMP***+Protein S deficiency	1	2.5
Idiopathic	5	12.8

* Methylenetetrahydrofolate reductase thermolabile variant. ** Antithrombin III.

*** Hypertrophic cardiomyopathy.

Loss of consciousness and focal or generalized convulsions were detected in 28.2% and 38.5% of patients during stroke attack, respectively. Of patients, 48.7% presented with right hemiparesis and 51.2% with left hemiparesis. Central facial paralysis accompanied in 25.6% of patients. Supportive treatment alone was applied in 18 patients; exchange transfusion was applied in four patients with SCA, aspirin in seven, low molecular weight heparin in six, both low molecular weight heparin and aspirin in three, and both heparin and streptokinase in one patient. Streptokinase was used in one patient with nephritic syndrome who admitted to hospital with in two hours of stroke in the acute phase. The other agents were given as both acute and prophylactic therapy in the situations of increased risk of recurrence. Among patients in whom no treatment were given, there was no recurrent stroke case. One of the patients with recurrent stroke was put on both heparin and aspirin in the acute phase and for prevention of recurrence, while the other was given both heparin for prevention and streptokinase in the acute recurrence, while the other was given both heparin for prevention and streptokinase in the acute phase.

Patients were followed for 4-96 months (mean: 38.73 ± 24.37 months). Only two cases (5.1%) had improved completely at the 18^{th} and 6^{th} month, respectively. The remainder had motor deficit of variable degrees. During follow-up, 60% of patients showed normal cognitive functions clinically while 40% varying degrees of impairment in cognitive functions.

Discussion

Ischemic cerebral events in children may be caused by many etiologic factors, such as cardiac, hematologic, metabolic, infectious, and inflammatory processes. Sometimes, it could be the first sign to occur depending on the underlying diseases. Especially in patients who have multiple risk factors of either hereditary or acquired origin, occurrence of stroke and risk of recurrence are increased. Epidemiologic studies have shown early recurrence risk in stroke at rates of 20 to 40%⁶⁻⁷. Recurrence risk of stroke varies from one population to another and, additionally, some risk factors may be predominantly seen in certain populations.

Risk factors in adults include age, hypertension, smoking, and diabetes mellitus. However, in childhood, completely different risk factors are reported. Congenital-acquired heart diseases, vascular anomalies, and SCA are the main risk factors. Apart from these, hypertension, diabetes mellitus, abnormalities in lipid metabolism, infections, trauma, and arterial dissections may be demonstrated. Hyperhomocysteinemia, coagulation disorders, antiphospholipid syndrome, anemia, and iron deficiency are some examples of other causes. In the literature, in 10 to 33% of cases, on etiological risk factor could be demonstrated^{2,8-10}. While the Canadian Pediatric Ischemic Stroke Registry¹¹ found SCA in 2% of cases, this ratio was 17% in a big metropolitan hospital in the USA¹². In the (Canadian group study, congenital-acquired heart diseases were shown as the most important risk factor. However, in another study, increased lipoprotein (a) level and deficiency of protein C type 1 were found as independent risk factors¹³. In our study, the most frequently seen etiologic factors were cardiac and infectious diseases. These were followed by MTHFR mutation (10.2%) and SCA (10.2%). In our region, SCA is commonly seen. Factor V Leiden mutation was found in only one case, and this was not high in comparison to the literature. Risk factors may vary from one population to another. Idiopathic cases accounted for 12.8% of all patents, and this was consistent with the literature. One of the two cases with recurrent stroke had dual pathology, namely hypertrophic cardiomyopathy and protein S deficiency, and the other had nephritic syndrome. Recurrent stroke was low in our study in comparison with the literature.

Even though no randomized controlled studies have been reported on the treatment of childhood stroke, treatment protocols used in adult stroke can also be applied to childhood stroke. Increased experience in antithrombotic and anticoagulant treatment in children shows that these agents may be used safely in childhood stroke. Low molecular weight heparin has been used as the first choice in arterial ischemic stroke. It is usually used in conditions with high emboli risk such as arterial dissection, coagulation disorders, and recurrent thrombosis14-16. Aspirin and other antiplatelet agents have been used as secondary prevention in arterial ischemic stroke¹⁷. Oral anticoagulant treatment, like warfarin, can be used in congenitalacquired heart diseases, severe hypercoagulability conditions, and arterial dissection¹⁸.

In approximately half of our cases, no treatment of any kind was applied, especially in the early cases, because of our poor experiences with the agents. Because of our increased experience in recent years, however, we thought these medications could be used safely. Aspirin to seven patients, heparin to six patients, and both heparin and aspirin to three patients were given. In four cases with SCA, exchange transfusion was performed. In only one case, both heparin and streptokinase were used. There were no side effects in any of the patients. One of the cases with recurrent stroke was given both heparin and aspirin, and the other was given both heparin and streptokinase; all cases without treatment had recurrences. Although our cases were small in number, we can conclude that risk of recurrent stroke may be affected more by underlying etiology rather than by treatment.

As a result, cardiologic and infectious causes appeared to be the most important etiologic factors, especially in our region. Etiologic factors rather than treatment used may play an important role in stroke recurrence.

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