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Risk Factors and Neurologic Outcomes in Childhood Arterial Ischemic Stroke

Akut Arterial İskemik İnmesi Olan Çocuklarda Risk Faktörleri ve Nörolojik Bulgular

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ÖZ

Amaç: Çalışmamızın amacı arterial iskemik inmesi (Aİİ) olan çocuklarda klinik özellikler, tedavi seçenekleri ve prognozun saptanmasıdır.

Materyal ve Metod: Çalışmamızda Aİİ tanısıyla merkezimizde 2009 ile 2015 yılları arasında takip edilen 102 çocuğun (62 kız ve 40 erkek) klinik bulguları retrospektif olarak değerlendirildi. Hastaların inme sırasındaki yaş ve cinsiyetleri, tıbbi geçmişleri, aile hikayesi, başvuru anındaki klinik buguları, epileptik nöbet hikayesi varlığı ve radyolojik bulguları kaydedildi. Merkezimizde Aİİ tanısı alan tüm çocuklara kardiyak inceleme, hematolojik ve immunolojik tesler, doğumsal metabolik hastalıklar için taramalar yapılmaktadır.

Sonuçlar: Aİİ'li hastalarda saptanan hastalıklar sırasıyla; kardiyak hastalık (25 hasta), geçici serebral iskemi (12 hasta), Down sendromu (11 hasta), Talasemi (9 hasta), Moyomoya hastalığı (7 hasta), homozigot MTHFR mutasyonu (6 hasta), homozigot faktör V Leiden mutasyonu (4 hasta), protein C eksikliği (3 hasta), orak hücreli anemi (1 hasta) ve 24 hastada altta yatan neden saptanamadı. Birden fazla risk faktörü 16 çocukta ve tekrarlayan inmeler 4 hastada saptandı. Hemipleji en sık saptanan klinik presentasyon (%88,2) iken, bunu nöbetler (%66,6) ve şuur değişikliği (%54,9) takip ediyordu. Ortalama klinik takip süresi 32,±5,4 idi. Aİİ'li 102 hastanın klinik takip sunuçları şu şekilde idi; asemtomatik 57,8%, kalıcı nörolojik defisit ya da epilepsi 40,2%, ölüm 2%.

Sonuçlar: Çalışmamızda Aİİ'li çocukların %76,5'sında altta yatan bir neden saptandı, hastaların %42.2'si öldü ya da motor ve/veya mental geriliği oldu ve aspirin profilaksisine rağmen 4 hastada tekrarlayan Aİİ atağı oldu.

Anahtar Kelimeler: Arterial iskemik inme, çocuk

ABSTRACT

Objective: The aim of this study is to describe clinical characteristics, treatment modalities and outcomes of children with arterial ischemic stroke (AIS).

Material and Methods: We retrospectively reviewed the charts of 102 children (62 girls and 40 boys) with AIS admitted at our hospital between 2009 and 2015. Age at stroke, sex, medical history, family history, clinical findings upon admission, history of seizure, and radiological findings were recorded. Cardiac assessment, hematological and immunological tests, metabolic screening were all performed in the patients.

Results: In 25 children stroke occured as a complication of cardiac disease, 12 had transient cerebral arteriopathy, 11 had Down's syndrome, 9 had thalassemia, 7 had moyamoya disease, 6 had MTHFR mutation, 4 had homozygote for factor V Leiden, 3 had protein C deficiency, 1 had sickle cell disease, and in 24 children no underlying cause could be found. Multiple risk factors were found in 16 children and recurrent stroke was observed in 4 patients. Hemiplegia was the commonest initial clinical presentation (88.2%) followed by seizure (66.6%) and decreased level of consciousness (54.9%). The avarage length of follow-up was 32.1±5.4 months. The outcome in all 102 stroke patients was as follows: asymptomatic 57.8%; persistent neurologic deficit or epilepsy 40.2%; and death 2%.

Conclusion: Our study showed an underlying cause for AIS in 76.5% of the patients; 42.2% of the patients either died or had motor and/or cognitive sequelae and recurrence occured despite prophylactic aspirin treatment in 4 patients.

Keywords: Arterial Ischemic Stroke, children

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Introduction

The World Health Organization's definition of stroke is a rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer, or leading to death.1 The incidence of pediatric stroke has been estimated at 2–3 cases per 100 000 children each year in North America and Europe, and has been increasingly recognized in children in recent years.2 The diagnosis and management of stroke are difficult because of the diversity of underlying risk factors and the absence of a uniform treatment approach. Stroke is classified into two major groups including hemorrhagic or ischemic, with arterial ischemic stroke (AIS) being slightly more frequent than hemorrhagic causes.

Pediatric AIS risk factors in children vary including congenital cardiac diseases, vasculopathies such as moyamoya disease (MMD), collagen tissue diseases, inborn errors of metabolism and inherited or acquired coagulation abnormalities that predispose to thrombotic complications.1,3 Recurence of stroke is higher when two or more risk factors exists in the same patient.4 Childhood AIS is a well recognized cause of neurologic morbidity in children, leading to cerebral palsy, epilepsy, and cognitive deficits.5,6 The objective of this study was to assess the risk factors, clinical presentations, etiologic factors, treatment modalities and outcomes, in a large, homogeneous cohort of children with AIS.

Material and Methods

This retrospective trial was conducted in 102 children with AIS who had admitted to Department of Pediatric Neurology between 2009-2015. A detailed perinatal history and family history were taken. The investigations performed on all patients at the time of diagnosis included: hematological tests (complete blood count, erythrocyte sedimentation rate, C-reactive protein, Hb electrophoresis, PT, aPTT, fibrinogen level, protein C, protein S level, and antithrombin III level), immunological tests (anticardiolipin, antinuclear antibody, rheumatoid factor and complement levels), metabolic screening (blood glucose level, electrolyte levels, liver and renal function tests, blood lactate, pyruvate and ammonia levels, serum amino acid level , serum homocysteine level, lipid and acylcarnitine profile, and urine organic acids. If an abnormal result was detected during the acute phase, the measurement was repeated 3 months later. Cardiac assessment including electrocardiogram and transthoracic or transesophageal echocardiography was performed in all patients. In addition, genetic tests including factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase (MTHFR) C677T mutations were conducted in 99 patients. In the 102 stroke patients, neuroimaging included: brain CT scan alone in 5, brain MR (MR) imaging alone in 75, and both studies in 22. Brain MR angiography was performed in 98 patients, 15 patients underwent conventional cerebral angiography. After discharge, neurologic examinations of the patients were conducted regularly in the pediatric neurology clinic, at 6-month intervals.

Exclusian criterias were perinatal stroke, hemorhagic stroke, transient ischemic attack, traumatic brain injury and neurological deficit resulting directly from an infective agent.

The institutional Medical Ethics Committee approved the study and all patients and guardians signed informed consent forms before participating in this clinical trial. Statistical analysis was performed using SPSS 17.0 for Windows. Summary statistics are presented as range and mean ± SD. All significant risk factors identified were reanalysed with multivariate logistic regression analysis.

Results

Totally 102 children with AIS (62 females and 40 males) were included in the study. The mean age at the time of presentation was 6.4 ± 2.1 years (range, 3.2 to 11.4 years). Hemiparesia (88.2%) was the most common presenting symptom, followed by seizure (66.6%), altered mental status (54.9%) and cranial nerve palsy (11.7%). Demographic and clinical symptoms and signs were summarized in Table 1.

Risk factors were present in 78 patients (76.5%). Cardiac disease (24.5%) was the most common reason, followed by transient cerebral arteriopathy (TCA) (11.8%), Down's syndrome 10.7%), thalassemia (9%), and MMD (7%) (Table 2). In 16 patients (15.6%) multiple risk factors were detected. Four children (4%) had recurrent AIS and the following combinations of risk factors were noted in these 4 children: MMD with cardiac disease (n=1) and talessemia with cardiac disease (n=1), Down's syndrome with MTHFR mutation and cardiac disease (n=1), and protein C deficiency with cardiac disease (n=1).

Antiplatelet (aspirin) therapy was used in 30, low-molecular-weight heparin (LMWH) therapy in 18, and both LMWH and aspirin was used in 9 patients during acute treatment. Streptokinase was performed in 1 patient with talessemia and cardiac disease. Prophylactic aspirin treatment was performed in 16 and warfarin in 1 patient.

Our follow-up period averaged 32.1±5.4 months (range, 23–48 months). One patient with MMD and 1 patient with cardiac disease died during acute attack and 59 (57.8%) of the children recovered completely at the end of 24 months. Twenty-nine (28.4%) children had varying degrees of hemiparesis and 10 (10%) children became mentally retarded. Nine of the 65 patients with seizure at the onset of stroke, later developed epilepsy (Table 1).

Table 1. Demographic and clinical data of subjects

Sex (female/male)	(62/40)	
Age at diagnosis (±SD)	6.4 ± 2.1 yr	
Initial neurologic findings	n	%
Hemiparesis	90	88.2
Seizure	68	66.6
Altered mental status	56	54.9
Cranial neuropathy	12	11.7
Acute therapy	n	%
Antithrombotic	1	1
Aspirin	30	29.4
LMWH	19	18.6
Aspirin+LMWH	9	9
Neurologic outcomes	n	%
Hemi-/tetraparesis	29	28.4
Cognitive decline	10	10
Epilepsy	9	9
Full recovery	59	57.8
Death	2	2
Stroke recurrences	4	4

LMWH: low-molecular-weight heparin

Table 2. Etiologic factors

	n	%
Cardiac disease	25	24.5
TCA	12	11.8
Down's Syndrome	11	10.7
Thalassemia major	9	9
MMD	7	7
MTHFR mutation	6	6
Factor V Leiden mutation	4	4
Protein C deficiency	3	3
Sickle cell anemia	1	1
Idiopathic	24	23.5

TCA: transient cerebral arteriopathy, MMD: Moyamoya Disease, MTHFR: methylenetetrahydrofolate reductase.

Discussion

Stroke in children and adolescents is a rare and also a complex condition that is associated with risk factors including cardiac, hematologic, metabolic, infectious, and inflammatory diseases.3,6,7 Approximately two-thirds of acute ischemic stroke cases occur in children with known risk factors. In our study, predisposing conditions were identified

in 76,5% of all stroke admissions. Our results are similar to those of other recent studies.4,8,9

A male predominance has been reported among pediatric ischemic stroke victims. By contrast, Kleindorfer et al. reported a male to female ratio of 0.8.10 Furtermore, Zahuranec et al. reported equal numbers of males and females.11 However, studies that corroborate a slight female predominance for ischemic stroke did exclude patients with a diagnosis of trauma.10 Our results of female predominance (female:male ratio of 1.6:1) may also be explained by the exclusion of trauma patients.

Risk factors associated with childhood AIS differ significantly from adults. The established vascular risk factors in adults related to atherosclerotic disease are relatively rare in children. In previous reports, up to 28% of ischemic strokes were attributed to cardiac disorders, frequently to congenital heart disease and cardiomyopathy.2,3,12 We found a cardiac risk factor in about 24.5% of patients with stroke. Therefore, cardiac evaluation remains essential in the investigation of childhood AIS.

Vasculopathies such as TCA and MMD have been identified in 18% to 80% of children with AIS.14,15 TCA is a monophasic arterial disease characterized by a unilateral focal or segmental stenosis involving the distal part of the internal carotid and the initial segments and branches of the anterior and/or middle cerebral artery followed by complete or partial resolution.15 We identified TCA in 11.8% and MMD in 7% of our patients with stroke. These findings underline the importance of vascular investigation in all arterial ischemic strokes in children. Although 44% of TCA cases are associated with varicella zoster infection, we identified varicella zoster only in 1 patient. A possible explanation for the pathogenesis of TCA is the inflammatory changes and thrombosis of cerebral vessels produced by stimulation of the superior cervical ganglion triggered by a non-specific infection of the head and neck. Lefond et al. found recent upper respiratory infection as an only predictor of TCA in children.16 In our study, a history recent upper respiratory infection was present in 10 out of 12 cases with TCA. However, minor infections are extremely common in young children, and yet most children do not have strokes. More study is needed to clarify how infection contributes to arteriopathies and stroke.

Prothrombotic disorders such as protein C and protein S deficiency, antithrombin III deficiency, factor V Leiden mutation, MTHFR mutation, factor XII deficiency, factor VIII deficiency, prothrombin 20210A mutations, and antiphospholipid antibodies have been found in approximately one-third of children with AIS.2-4,7 In the present study, 6 children had MTHFR mutation, 4 children had factor V Leiden mutation and 3 children had protein C deficiency. Detection of acquired and congenital prothrombotic disorders is important because this information can influence both initial and long-term therapies. In addition, family studies are indicated if a child has a congenital prothrombotic disorder. Affected patients and the family members require counseling regarding risk factors for thrombosis, and the need for intermittent prophylaxis in the presence of acquired risk factors. Further studies are required to define the significance of these abnormalities in childhood AIS.

The general rate of stroke recurrence is between 5% and 30%, and is higher among children with identified multiple risk factors.3,7-9 Our stroke recurrence rate was 4%, and lower than the recurrence rate previously reported. Our relatively shorter follow-up period and small number of subjects than other studies might be the reason. In our series, all the recurrences have been linked to multiple risk factors. Although, the number of recurrent strokes in our patients was not enough to show a relation between cardiac diseases and recurrent AIS, it is interesting that cardiac disease was present as a risk factor in

all recurrences.

Many of the treatment approaches have been adapted from studies in adults or from the results of small, non-randomized pediatric studies. We administered thrombolytic therapy only in 1(1%) patient. Other investigators have also reported low rates of thrombolytic administration (2-4%) in pediatric stroke victims.6,9,13 Limited use of thrombolytic therapy may be explained by delayed diagnosis and lack of safety and efficacy studies. Aspirin is frequently used as the treatment of choice for secondary prevention of AIS in situations of increased risk of recurrence such as cerebral arterial stenosis. Major uses of warfarin treatment in children include congenital or acquired heart disease, severe hypercoagulable states and arterial dissection.18 In our study, most of the children with AIS are placed on aspirin for prophylaxis in order to minimize the side effects due to warfarin. However, all of four patients had recurrent AIS while on aspirin prophylaxis. Large controlled clinical trials are required to establish the role of antithrombotics and other therapies on the role of prophylaxis.

Assessment of short and long-term outcomes of infants with AIS shows that multiple, severe neurologic deficits are frequent, but the estimated incidence rates vary widely according to the studied populations. Goldenberg et al. found that, after AIS, 74% of patients had neurologic deficits at hospital discharge.17 In a Swiss study, 65% of the children with AIS had long-term neurological impairment.19 Furthermore, the reported pediatric stroke mortality rates are between 2-9%.6,7,17,19 However, we found a lower mortality rate (2%) and a lower neurologic sequele rate (42.4%) in our study. This may be due, in part, to different co-morbidities in our cohort. Another explanation may be the exclusion of the patients with trauma and CNS infection.

This study does have limitations. One, this study was conducted at a single center and involved a relatively small sample size. Second, our study was a prospective trial with a relatively short observation period. The possibility cannot be excluded that some children with hemiplegia in early childhood may no longer have motor disabilities later, because of brain plasticity. However, 2 years is a widely accepted age at which to evaluate gross motor function in children, and a large change in motor status is improbable.

In conclusion, the present study confirms that AIS in children is frequently associated with a genetic and/or acquired predisposing conditions and with the presence of multiple risk factors. As all of the recurrences occured while on aspirin prophylaxis, cohorts to determine the optimal treatment of secondary prevention and risk factor modification are critically needed.

References

1. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, Ferriero D, Jones BV, Kirkham FJ, Scott RM, Smith ER.. A scientific statement from a special writing group of the American Heart Association Stroke Council and the Council of Cardiovascular Disease in the Young. Stroke. 2008;39: 2644-91.

2. de Veber G, Roach ES, Riela AR, Wiznitzer M. Stroke in children: recognition, treatment, and future directions. Semin Pediatr Neurol 2000;7:309-17.

3. Simma B, Martin G, Müller T, Huemer M. Risk factors for pediatric stroke: consequences for therapy and quality of life. Pediatr Neurol. 2007;37:121-6.

4. Touré A, Chabrier S, Plagne MD, Presles E, des Portes V, Rousselle C. Neurological outcome and risk of recurrence depending on the anterior vs.posterior arterial distribution in children with stroke. Neuropediatrics. 2009;40:126-8.

5. Westmacott R, Askalan R, MacGregor D, Anderson P, Deveber G. Cognitive outcome following unilateral arterial ischaemic stroke in childhood:effects of age at stroke and lesion location. Dev Med Child Neurol. 2010;52:386-93.

6. Incecik F, Ozlem Hergüner M, Altunbasak S. Risk factors and treatment outcomes for children with arterial ischemic stroke. J Clin Neurosci. 2010;17:1000-2.

7. Lopez-Vicente M, Ortega-Gutierrez S, Amlie-Lefond C, Torbey MT. Diagnosis and management of pediatric arterial ischemic stroke. J Stroke Cerebrovasc Dis. 2010;19:175-83.

8. M. Steinlin, I. Pfister, J. Pavlovic, Everts R, Boltshauser E, Capone Mori A, Gubser Mercati D, Hänggeli CA, Keller E. The first three years of the Swiss Neuropaediatric Stroke Registry (SNPSR): a population-based study of incidence, symptoms and risk factors. Neuropediatrics. 2005;36: 90–97.

9. Tham EH, Tay SK, Low PS. Factors predictive of outcome in childhood stroke in an Asian population. Ann Acad Med Singapore. 2009;38:876-81.

10. Kleindorfer D, Khoury J, Kissela B, Alwell K, Woo D, Miller R, Schneider A, Moomaw C, Broderick JP. Temporal trends in the incidence and case fatality of stroke in children and adolescents. J Child Neurol. 2006;21:415-8.

11. Zahuranec DB, Brown DL, Lisabeth LD, Morgenstern LB. Is it time for a large, collaborative study of pediatric stroke? Stroke. 2005;36:1825-9.

12. Neil Friedman. Pediatric cardiovascular disease and stroke. J Pediatr Neurol. 2010;8: 259-265 259.

13. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics. 2007; 119:495–501.

14. Braun KP, Bulder MM, Chabrier S, Kirkham FJ, Uiterwaal CS, Tardieu M, Sébire G. The course and outcome of unilateral intracranial arteriopathy in 79 children with ischaemic stroke. Brain 2009; 132:544-557.

15. Miravet E, Danchaivijitr N, Basu H, Saunders DE, Ganesan V. Clinical and radiological features of childhood cerebral infarction following varicella zoster virus infection. Dev Med Child Neurol 2007;49:417-422.

16. Amlie-Lefond C, Bernard TJ, Sébire G, Friedman NR, Heyer GL, Lerner NB, DeVeber G, Fullerton HJ. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the International Pediatric Stroke Study. Circulation. 2009;119:1417-23.

17. Goldenberg NA, Bernard TJ, Fullerton HJ, Gordon A, deVeber G. Antithrombotic treatments, outcomes, and prognostic factors in acute childhoodonset arterial ischaemic stroke: a multicentre, observational, cohort study. Lancet Neurol 2009;8:1120-1127.

18. Monagle P, Chalmers E, Chan A, Veber G, Kirkham F, Massicotte P, Michelson AD. Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2008;133:887-968.

19. Christerson S, Strömberg B. Stroke in Swedish children II: long-term outcome.Acta Paediatr. 2010;99:1650-6.