Clinical Presentation And Prothrombotic Risk Factors İn Neonatal And Childhood Stroke: A Retrospective Study.

Yenidoğan Ve Çocukluk Çağı İnmelerinde Klinik Ve Protrombotik Risk Faktörleri: Bir Retrospektif Araştırma

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ABSTRACT

AIM: Neonatal and childhood stroke has high morbidity and mortality, associates with co-morbid conditions, it is difficult to diagnose and the treatment is uncertain. We aimed to examine epidemiology and long term outcomes of childhood stroke patients, followed our department.

MATERIALS AND METHODS:

A retrospective study of enrolled pediatric stroke patients at a pediatric hematology department of a Children's Hospital. The disease presentations, prothrombotic risk factors, co-morbid conditions, stroke-related death or neurological deficits of the children followed-up with stroke diagnosis were recorded.

RESULTS:

A total of 115 children (min-max: 0-16.8 years, median age of diagnosis: 2 years, 49.6% girls) were included. Paresis or plegia (56.5%), convulsions (43.5%), and cranial nerve palsies (10.4%) were most common presentations. Co-morbid conditions were common (69%); the most common were infections (22.6%) and congenital cardiac diseases (20.8%). In 47.7% of the patients who presented with paresis or plegia, stroke was diagnosed within 30 days after stroke; the rest was diagnosed later. Among the determined prothrombotic risk factors, elevated homocysteine levels were the most common (27%), followed by factor V G1691A mutations (20%), and elevated lipoprotein (a) (19.1%) levels. Neurological sequel rate was 62.5%. Mortality rate was 2.6%.

CONCLUSIONS:

Childhood stroke is associated with a variety of co-morbid conditions and hereditary and acquired prothrombotic risk factors. Stroke in children has a high sequel rate. We think that, delayed diagnosis and treatment in our study group could be the reason for this result.

Key words: *Child, Stroke, Intracranial embolism and thrombosis.*

AMAÇ:

Yenidoğan ve çocukluk çağı inmelerinde, morbidite ve mortalite oranları yüksektir. Komorbid durumlar eşlik etmektedir, tanı koymak zordur ve tedavisi kesinlik kazanmamıştır. Amacımız, ünitemizde takip edilen çocukluk çağı inme hastalarımızda, epidemiyoloji ve uzun dönem takip sonuçlarını araştırmaktır.

MATERYAL VE METOD:
Bir retrospektif araştırmada, bir Çocuk Hastanesinin Pediatrik Hematoloji Bölümündeki pediatrik inme hastaları çalışmaya alındı. İnme nedeniyle başvuran takipli çocukların ilk başvuruda klinik bulguları, protrombotik riskler, komorbiditeler, inme nedeniyle ölüm ya da nörolojik sekel kaydedildi.

BULGULAR:
Toplam 115 çocuk (min-max: 0-16.8 yıl, median tanı yaşı: 2 yıl, %49.6 kız) çalışmaya alındı. Parezi veya pleji (%56,5), konvülziyon (%43.5), ve kafa çifti tutulumu (%10,4) en sık başvuru bulgularıydı. Komorbid durumlar sık olup (%69), en sık olarak enfeksiyomlar (%22,6) ve konjenital kalp hastalıkları (%20,8) saptandı. Parezi veya pleji ile başvuran hastaların %47,7'sinde inme tanısı 30 gün içinde konabildi, diğer hastalar daha geç dönemde tanı aldı. Saptanan protrombotik risk faktörleri arasında artmış homosistein düzeyi en sık olup (%27), bunu faktör V G1691A mutasyonu (%20), ve artmış lipoprotein (a) (%19,1) düzeyi izlemekteydi. Nörolojik sekel oranı %62,5 bulundu. Mortalite oranı %2,6 idi.

SONUÇ:
Çocukluk çağı inmelerine birçok değişik komorbid durumlar ve herediter ve kazanılmış protrombotik risk faktörleri eşlik etmektedir. Çocuklarda inme yüksek sekel oranına sahiptir. Tanı ve tedavideki gecikmenin bizim çalışmamızda bu sonuca neden olduğunu düşünmekteyiz.
Anahtar Kelimeler: Çocuk, İnme, Kafaiçi emboli ve tromboz

INTRODUCTION
Pediatric stroke is divided into ischemic and hemorrhagic stroke. Ischemic stroke is a focal damage to an area of brain tissue within a vascular territory due to loss of blood flow or oxygenation, and represents 55% of pediatric strokes. It is subdivided into arterial ischemic stroke (AIS), which is due to loss of arterial flow, or venous infarction, which is due to loss of flow in a draining cerebral vein or venous sinus by a clot, called cerebral sinovenous thrombosis (CSVT), leading to an infarcted brain parenchyma (1).
Trombus formation may result from hypercoagulable states. It also develops in response to endothelial damage, such as inflammation or vasculopathy. Thromboembolism, however, occurs when a clot formed elsewhere in the body, such as the heart, in the presence of a venous-to-arterial shunt, travels and becomes lodged in a cerebral artery. Hemorrhagic stroke includes spontaneous hemorrhage within the brain parenchyma or subarachnoid hemorrhage (1).
Incidence of stroke in children are increasing, due to many factors like extensive usage of invasive vascular procedures in critically ill children and their better survival from previously lethal disorders. In recent years, clinicians are more aware of thrombosis in pediatric patients because of the improvement and availability of the sensitive imaging techniques (2-4). The clinical manifestations of childhood stroke can be life-threatening, or cause neurological deficits in approximately 60%, and recurrence (10%-25%) (4). The symptoms and signs are non-specific and this often causes delayed diagnosis or diagnosis can completely be missed. Unavailability of advanced brain imaging techniques at an urgent basis, such as magnetic resonance imaging (MRI) is a reason of delayed diagnosis or therapy (2, 4-6).
The purpose of our study was to determine the clinical presentations, associating prothrombotic risk factors, diseases or conditions, and outcomes of childhood stroke cases, who were followed up at our Hospital's Pediatric Hematology Department.

MATERIALS AND METHODS
After obtaining approval from the Hospital's Ethics Committee (Approval number: 2012 / 025), childhood stroke cases were examined, retrospectively, between 1 January 2010 to 1 January

2015 at the Department of Pediatric Hematology, Ankara Children's Hematology and Oncology Hospital. The informations were diagnosis age, follow-up period, signs and symptoms at first presentation, associating prothrombotik risk factors, chronic diseases and clinical conditions.

Perinatal stroke means a focal disruption of cerebral blood flow between 20 weeks of fetal life through the 28th postnatal day confirmed by neuroimaging studies. It typically presents acutely in the neonatal period, often with symptomatic seizures. Presumed perinatal stroke, refers to patients who do not present until later in the first year of life, often with an emerging hemiparesis. In these cases, stroke is retrospectively diagnosed by the presence of a chronic infarct on neuroimaging. When pediatric stroke occurs outside of the perinatal period, which is typically defined as anything beyond the first month of life, the term childhood stroke is used (7).

In this study, prothrombotic risk factors were compared according to three different age groups: Group 1: Infants <28 days, group 2: Infants in the first year of life and Group 3: Children beyond the first year at the time of stroke diagnosis. All the cases had been tested for fibrinogen, protein C, protein S, antithrombin, homocysteine, lipoprotein a [Lp (a)], anticardiolipin, antiphospholipid antibodies, factor VIII, IX, XI, factor V G1691A, prothrombin G20210A and methylenetetrahydrofolate reductase (MTHFR) polymorphisms. Comparison of reference ranges for all tested coagulation factors were assessed according to age specific data (8-9). Neuroimaging methods for diagnosis were conventional MRI, diffusion MRI, MRI angiography, and/or MRI venography.

Statistical analysis was performed by using Statistical Packet for Social Sciences version 16.0. Kolmogorov Smirnov test was used for normality of continuous or discontinuous numerical variables. Age distribution of children and follow-up period were summarized with descriptive statistics, expressed as medians (min-max). For categorical data, frequency distributions were compared between groups by chi-square test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Among 115 cases, 49.6% (n=57) were girls [Median diagnosis age 2 years (min-max=7 days-16.8 years)]. Stroke was arising from arterial system in 44.3% (n=51), venous system in 19.1% (n=22) and in 36.5% (n=42), cause of the infarct was not explained from which system it originated.

Most common clinical presentations were paresis/plegia (56.5%, n=65) and seizures (36.5%, n=42) (Table 1). In newborns, apnea/cyanosis (38.5%) was common (P=0.001).

Infection history was noted in 22.6% (n=26) and a co-morbid condition associated in 68.7% (n=79). Cardiac diseases (26%, n=30) were most common, being more frequent in newborns (46.2%) (p=0.035). Co-morbid conditions are represented in Table 2.

Prothrombotic risk factors are represented in Table 3. In newborns, low antithrombin 3 levels (23.1%) (p=0.017) and higher homocysteine (61.5%) were detected (p=0.015).

In 32 (27.8%) of childhood strokes, intracranial hemorrhages associated to infarcts. Nine of them had CSVT, and in 12 obstruction was detected at cerebral arteries (p>0.05).

Imaging showed that infarcts originated from posterior circulation in eight of the children. The infarcts also originated from both anterior and posterior circulation, basilar artery, bilaterally internal carotid and basilar artery, left vertebral artery and basilar artery. In 94 (81.7%) patients, infarct originated from anterior circulation. In eight patients with CSVT an evidence of an infarct was not observed.

In eight (7%) of the childhood strokes, recurrent attacks occurred. One of the children with recurrence died.

DISCUSSION

In pediatric stroke cases, the diagnosis is often delayed and many are not receiving appropriate treatment. Today, it is adviced to care these patients in pediatric stroke centers. In this study, we aimed to discover the characteristic clinical findings and prothrombotic risk factors of stroke patients.

The most frequent symptoms at initial diagnosis were plegia, paresis and convulsions (Table 1). Clinical hallmark of pediatric stroke is sudden-onset focal neurologic deficits (1), including hemiparesis, plegia, speech disturbance or convulsions. These are usually attributed to migraine, epilepsy or encephalitis rather than stroke, and this often causes delayed diagnosis (10). Neurological findings vary according to age groups (11, 12). Seizure, including up to 46% of younger children, is seen in 5% of adult strokes (1). Apnea, convulsion, lethargy are mainly noted in neonates (11, 12). In our study also, apnea was mostly observed in neonates. Speech or language problems, sensory and visual disturbance are remarkable in school children (11, 12). In our group, sensory and visual disturbances were more frequent in older children (13%). Intracranial hemorrhages associated to childhood stroke in 27.8% of our patients, 28% had CSVT. In the literature cerebral hemorrhage development was reported in one third of venous infarcts (13).

In literature, chronic diseases that increase stroke risk in childhood are congenital heart disease (CHD), hematological, vascular and infectious diseases (14, 15), with the prevalence of 71%-100% (10, 11). In our group, chronic diseases and co-morbid conditions associated to majority of childhood stroke. Among these, CHD and infections were most frequent.

Hereditary prothrombotic abnormalities are reported at 20%-50% in AIS and 33%-99% in CSVT, in childhood stroke (16, 17). We determined at least one prothrombotic risk factor in 67%. Elevated homocysteine levels were the most common.

In our study, FV 1691 mutation was identified in 20% of childhood strokes. Akar et al. (18) identified FV1691 GA in 25% of children with cerebral infarcts and stated it as an independent risk factor.

High Lp (a) levels is a risk factor for premature myocardial infarction and stroke in adults (19). In children, there are limited number of studies (17). In our cases, we determined high Lp (a) levels in 19.1%.

Prothrombin G20210A mutation is present in 1%-2% of the healthy population and 5%-6% in venous thrombosis (20, 21). We determined prothrombin G20210A mutation in 5.2% of patients.

Antithrombin deficiencies are reported to have no difference in frequencies, in newborns and older children (17). However, in our study, we determined antithrombin deficiency more frequently in newborns.

In 62.6% of our children, there were neuromotor deficits. In literature, long-term neurologic sequel rates were reported up to 70% in children with stroke (2).

In eight (7%) of our cases, recurrent attacks occurred. Recurrent CSVT and AIS in neonates were reported between 8%-17%, and approximately 3% or, also reported to be up to 19-40% in older children (2).

In this study we observed that newborn and childhood stroke is associating with prothrombotic risks and co-morbid conditions. Cases present with neurological symptoms mainly, but might present with other symptoms. Patients have a sequel lasting lifelong. Therefore, early diagnosis and treatment is very important. However, early diagnosis needs advanced imaging methods to be present in emergency conditions.

We should improve knowledge of us about risk factors that could provide to assess taking necessary precautions in patients at risk for occurrence of stroke. Multicenter studies are necessary to establish the predictors of adverse outcome of death or neurologic deficit.

Diagnostic difficulties, uncertainty of most appropriate treatment, high neurological sequel rates and the burden of disease to family and community are issues needed to be resolved.

References

1. *Bernson-Leung ME, Rivkin MJ. Stroke in Neonates and Children. Pediatr Rev. 2016;37(11):463-77. PMID: 27803143; doi: 10.1542/pir.2016-0002.*
2. *Pipe SW, Goldenberg NA. Acquired disorders of hemostasis. In Nathan DG, Orkin SH, Ginsburg D, et al. Nathan and Oski's Hematology of Infancy and Childhood. 7th ed.* ***Philadelphia:*** *WB Saunders; 2009. p. 1591-620.*
3. *deVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001;345(6):417-23. PMID: 11496852; doi: 10.1056/NEJM200108093450604.*
4. *deVeber G. In pursuit of evidence-based treatments for paediatric stroke: the UK and Chest guidelines. Lancet Neurol. 2005;4(7):432-6. PMID: 15963446; doi: 10.1016/S1474-4422(05)70120-4.*
5. *Bernard TJ, Goldenberg NA. Pediatric arterial ischemic stroke. Hematol Oncol Clin North Am. 2010:24(1);167-80. PMID: 20113901; doi: 10.1016/j.hoc.2009.11.007.*
6. *Se´bire G, Tabarki B, Saunders DE, et al. Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. Brain. 2005;128(Pt 3):477-89. PMID: 15699061; doi: 10.1093/brain/awh412.*
7. *Felling RJ, Sun LR, Maxwell EC, Goldenberg N, Bernard T. Pediatric arterial ischemic stroke: Epidemiology, risk factors, and management. Blood Cells Mol Dis. 2017;67:23-33. PMID: 28336156; doi: 10.1016/j.bcmd.2017.03.003.*
8. *Brugnara C. Appendices: Reference Values in Infancy and Childhood. In Nathan DG, Orkin SH, Ginsburg D, et al. Nathan and Oski's Hematology and Oncology of Infancy and Childhood. 7th ed. Philadelphia: WB Saunders; 2009. p. 1769-96.*
9. *Altuntaş N, Soylu K, Suskan E, Akar N. Homocysteine levels in Turkish children. Turk J Haematol. 2004;21(2):79-82. PMID: 27263843*
10. *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(3):175-183. PMID: 20434043; doi: 10.1016/j.jstrokecerebrovasdis.2009.03.013.*
11. *Witmer C, Ichord R. Crossing the blood-343 brain barrier: clinical interactions between neurologists and hematologists in pediatrics-advances in childhood arterial ischemic stroke and cerebral venous thrombosis. Curr Opin Pediatr. 2010;22(1):20-7. PMID: 19996969; doi: 10.1097/MOP.0b013e3283350d94.*
12. *Gabis LV, Yangala R, Lenn NJ. Time lag to diagnosis of stroke in children. Pediatrics. 2002;110(5):924-8. PMID: 12415031*
13. *Pongmoragot J, Saposnik G. Intracerebral hemorrhage from cerebral venous thrombosis. Curr Atheroscler Rep. 2012;14(4):382-9. PMID: 22664979; doi: 10.1007/s11883-012-0260-1.*
14. *deVeber G. Risk factors for childhood stroke: little folks have different strokes! Ann Neurol. 2003;53(2):149-50. PMID: 12557279; doi: 10.1002/ana.10461.*
15. *Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G. Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. Stroke. 2009;40(1):52-7. PMID: 18787197; doi: 10.1161/STROKEAHA.108.521203.*
16. *Barnes C, Deveber G. Prothrombotic abnormalities in childhood ischaemic stroke. Thromb Res. 2006;118(1):67-74. PMID: 16039697; doi:10.1016/j.thromres.2005.05.021.*
17. *Kenet G ,Lütkhoff LK, Albisetti M, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. Circulation. 2010;121(16):1838-47. PMID: 20385928; doi: 10.1161/CIRCULATIONAHA.109.913673*
18. *Akar N, Akar E, Deda G, Sipahi T, Orsal A. FactorV1691 G-A, prothrombin 20210 G-A, and methylenetetrahydrofolate reductase 677 C-T variants in Turkish children with cerebral infarct. J Child Neurol. 1999;14(11):749-51. PMID: 10593555; doi: 10.1177/088307389901401113*

19. *Rosenson RS, Stein JH, Durrington P, Freeman MW (Ed), Saperia GM (Ed). Lipoprotein(a) and cardiovascular disease. UptoDate. April 29, 2013. Available at: https://www.uptodate.com/contents/lipoprotein-a-and-cardiovascular-disease/print*
20. *Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996;88(10):3698-703. PMID: 8916933*
21. *Cumming AM, Keeney S, Salden A, et al. The prothrombin gene G20210A variant: Prevalence in a UK anticoagulant clinic population. Br J Haematol. 1997;98(2):353-5. PMID: 9266933*

Table 1: Clinical manifestations of childhood stroke

Clinical manifestations	N (%)
Paresis/plegia	65 (56.5)
Seizures	42 (36.5)
Cranial nerve paralysis	12 (10.4)
Loss of consciousness/respiratory-circulatory failure	11 (9.6)
Pseudotumor cerebri	8 (7)
Seizures + fever	8 (7)
Apnea/cyanosis	6 (5.2)
Acute headache	4 (3.5)
Vomiting	3 (2.6)
Ataxia, tremor	3 (2.6)
Speech disturbance	2 (1.7)
Gastroenteritis, vomiting, dehydration	2 (1.7)
Chronic headache	2 (1.7)
Others (Hypertension, blurred vision, vertigo, nystagmus, chest pain)	8 (7)

Table 2: Chronic diseases and other clinical conditions in childhood stroke

Diagnosis	N (%)
Nephrological (Nephrotic syndrome, familial mediterranean fever, henoch schonlein purpura….)	11 (9.6)
Hematological (Sickle cell anemia, acute lymphoblastic leukemia, congenital dyserithropoetic anemia, thrombocytosis, vitamin B12 deficiency, thalassemia….)	12 (10.4)
Neurological (Neurofibromatosis, epilepsy….)	5 (4.3)
Cardiac (Congenital heart disease, hypertrophic cardiomyopathy…)	30 (26)

Other (Trauma, catheter …)	21 (18.3)
Total	79 (68.7)

Table 3: Prothrombotic risk factors in children childhood stroke

Prothrombotic risk factors	n(%)
Hyperhomocysteinemia	31 (27)
FV G1691A mutation	23 (20)
Increased lipoprotein (a)	22 (19.1)
Antithrombin deficiency	7 (6)
Increased FVIII	7 (6)
Protrombin G20210A	6 (5.2)
Anticardiolipin/Antiphospholipid antibody	3 (2.6)
Protein C deficiency	3 (2.6)
Protein S deficiency	3 (2.6)
Increased fibrinogen	4 (3.5)
Increased FIX	2 (1.7)
Increased FXI	1 (0.9)
No risk factor	38 (33)

Flow-diagram: Enrolment characteristics of pediatric stroke patients that have been regularly followed in Pediatric Hematology Department of the Children's Hospital.