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Evaluation of perinatal arterial ischemic stroke patients: A single center experience

Perinatal arteriyel iskemik inme hastalarının değerlendirilmesi: Tek merkez deneyimi

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Abstract

Aim: Perinatal arterial ischemic stroke (PAIS) is the one of the frequent causes of morbidity and neurologic disability, such as unilateral cerebral palsy (UCP), epilepsy and neurodevelopmental deficiencies. The aim of this study is to determine the clinical characteristics, risk factors and long term outcomes of PAIS patients.

Methods: This retrospective cohort study was conducted with 49 PAIS patients who were followed up in the Pediatric Neurology Department between January 2009 and September 2015. Clinical data including demographic features, gestational history, age at diagnosis, initial clinical presentation, brain MRI features, perinatal risk factors and long-term outcome were collected from patient files.

Results: The study group comprised 30 females and 19 males with a mean age of 6.3 (4.5) years. Twin pregnancy (6.1%), intrauterine growth retardation (IUGR) (8.2%), peripartum asphyxia (8.2%) and presentation abnormality (6.1%) were the most common maternal / neonatal risk factors. The most common prothrombotic risk factors were MTHFR mutations (42.85%), followed by FVL mutations (16.32%). The epilepsy rate was 73.3%, 6.4% of which had refractory epilepsy. All patients had UCP.

Conclusions: Risk factors and their roles in development of PAIS have not been fully established. According to this study, most of the PAIS patients have at least one or more maternal, neonatal or prothrombotic risk factors, and all patients have motor and cognitive impairment related with PAIS. Multi-center prospective studies with more cases are needed to fully enlighten the causes of this disease and to develop preventive measures.

Keywords: Perinatal, Neonatal, Ischemic, Stroke, Epilepsy

Öz

Amaç: Perinatal arteriyel iskemik strok (PAIS), unilateral serebral palsi (UCP), epilepsi ve nörogelişimsel bozukluklar gibi morbidite ve nörolojik hastalığın sık nedenlerinden biridir. Bu çalışmanın amacı, PAIS hastalarının klinik özelliklerini, risk faktörlerini ve uzun vadeli sonuçlarını belirlemektir.

Yöntemler: Bu retrospektif kohort çalışma, Ocak 2009-Eylül 2015 tarihleri arasında Çocuk Nörolojisi Bölümünde takip edilen 49 PAIS hastası ile yapılmıştır. Demografik özellikler, gebelik öyküsü, tanı yaşı, ilk klinik bulgu, beyin MRG bulguları, perinatal risk faktörlerini ve uzun vadeli sonuçları hasta dosyalarından toplandı.

Bulgular: Çalışma grubu yaş ortalaması 6,3 (4,5) yıl olan, 30 kadın ve 19 erkekten oluşmuştur. İkiz gebelik (%6,1), intrauterin büyüme geriliği (IUGR) (%8,2), perpartum asfiksi (%8,2) ve prezentasyon anormallikleri (%6,1) en sık görülen maternal / neonatal risk faktörleri idi. En yaygın protrombotik risk faktörleri ise MTHFR mutasyonları (%42,85) ve FVL mutasyonlarıydı (%16,32). Hastalardaki epilepsi oranı %73,3 olarak saptandı ve bu hastaların % 6,4'ünde dirençli epilepsi vardı. Tüm hastalar unilateral serebral palsi tanısı ile izleniyordu.

Sonuç: PAIS risk faktörleri ve bu risk faktörlerinin PAIS gelişimindeki rolleri tam olarak belirlenmemiştir. Bu çalışmaya göre, PAIS hastalarının çoğunda en az bir veya daha fazla maternal, neonatal veya protrombotik risk faktörü bulunmaktadır. Ve tüm hastalarda PAIS ile ilgili motor ve bilişsel bozukluk vardır. Bu hastalığın nedenlerini tam olarak aydınlatmak ve önleyici tedbirler geliştirebilmek için daha fazla vaka içeren çok merkezli prospektif çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Perinatal, Yenidoğan, İskemik, İnme, Epilepsi

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Introduction

Perinatal arterial ischemic stroke (PAIS) is an important cause of chronic neurological morbidity such as cerebral palsy (CP), epilepsy, cognitive dysfunction, language and behavioral problems [1]. PAIS occurs in an estimated 1:2300-4000 term births [1,2]. PAIS may cause no symptoms or subtle or nonspecific symptoms, therefore the age of diagnosis of PAIS varies. It is divided into 3 groups according to the age of diagnosis. Fetal stroke is diagnosed before birth by fetal imaging methods or in stillbirths on the basis of neuropathological examination, neonatal stroke is diagnosed after birth and on or before the 28th postnatal day, presumed perinatal stroke is diagnosed in infants >28 days of age but in whom the event is presumed to have taken place between the 20th week of gestation and the 28th postnatal day [3,4]. In the newborn period, PAIS mostly presents with seizures. There may also be signs and symptoms of neonatal encephalopathy such as lethargy, hypotonia, feeding difficulties, or apnea. Presumed PAIS is diagnosed when children present with a focal hand weakness (or early handedness), seizures or global developmental delay [3,5].

The etiology of PAIS remains unclear. Various maternal and neonatal risk factors have been identified in previous studies such as preeclampsia, maternal fever, small for gestational age, oligohydramnios, birth asphyxia, hypoglycemia, chorioamnionitis, twin pregnancy, congenital heart diseases, low Apgar score and peripartum asphyxia [5-7]. Genetic disorders may play a role in the pathogenesis of PAIS. Prothrombotic risk factors including MTHFR and factor V Leiden mutation, elevated lipoprotein (a), prothrombin gene mutation, and protein C deficiencies can be associated with PAIS [8,9].

This study focuses on neonatal and presumed perinatal arterial ischemic stroke. The aim of this study was to identify risk factors, clinical presentations, and neurodevelopmental outcomes of PAIS.

Materials and methods

This study was performed retrospectively on 49 perinatal arterial ischemic stroke patients who were diagnosed and followed at Eskisehir Osmangazi University Hospital, Department of Pediatric Neurology between January 2009, and September 2015. The principles of the Declaration of Helsinki were abided. Written informed consent was obtained from each of the parents and/or legal representatives before the patient's inclusion in the study.

This study included neonatal and presumed PAIS patients. The diagnoses of neonatal and presumed PS were based on clinical features, neurological examinations, and cranial magnetic resonance imaging (MRI) findings. Inclusion criteria were term birth, PS confirmed with neuroimaging (magnetic resonance imaging (MRI)) and a follow-up of more than 12 months. Exclusion criteria included cortical dysplasia, congenital cerebral anomaly, brain tumor, sequela of hypoxic ischemic encephalopathy, central nerve system infection, cerebrovascular disorders, or trauma.

The patients' following data were obtained by evaluating hospital files retrospectively using a standard form: Consanguineous marriage, number of pregnancies, age of pregnancy, detailed prenatal and natal history, perinatal stroke types, age of first symptoms, age at the time of diagnosis, maternal-fetal risk factors, neuroimaging findings and clinical features.

Among the laboratory data, the following thrombophilic screening tests were obtained from the patient files retrospectively: Protein C and S, antithrombin III (ATIII), lipoprotein (a), homocysteine, factor VIII levels, anticardiolipin antibodies and lupus anticoagulant, methylenetetrahydrofolate reductase (MTHFR) mutations (C677T and/or A1298C), factor V Leiden mutation(FVL) and prothrombin G20210A mutation.

Cranial MRI examinations were performed on admission at 1.5 Tesla at different institutions using T1- and T2-weighted spin-echo, and inversion recovery sequences in the axial, sagittal and coronal planes.

Results

A total of 49 patients were enrolled in the study (61.2% females, 38.8% males). The mean age of the patients was 6.36 (4.5) years, with a range of 1-17 years. Thirty-two patients (65.3%) were presumed to have perinatal stroke, and 17 patients (34.7%) were diagnosed with neonatal perinatal stroke. Thirty-three (67.3%) patients had right, and 16 (32.7%) patients had left hemiplegia. The average duration of follow-up was 4.2 years (range: 1–15 years).

Consanguineous marriage was present in 18.4% of parents. About 10.2% of the pregnant women were under 20 years of age, 12.2% were over 35 years of age and 40.8% had the first pregnancy. Among all, 63.3% patients were born with spontaneous vaginal delivery and 37.7% with caesarian section. One mother (2%) had chronic hypertension and one had multiple sclerosis (2%). Twin pregnancy was present in 6.1% of patients and 41.5% were the first pregnancy. Other maternal/fetal risk factors were as follows: Intrauterine growth retardation (IUGR) (8.2%), gestational diabetes, peripartum asphyxia (8.2%), presentation abnormality (6.1%), preeclampsia (4.1%), abnormal vaginal bleeding (4.1%), fetal heart rate abnormality (4.1%), and emergency cesarean delivery (4.1%). Prothrombotic risk factors were detected in 73.5% of the patients. The most common prothrombotic risk factors were MTHFR mutations (42.85%), followed by FVL mutations (16.32%). Co-existence of MTHFR and FVL mutations were detected in 8.2% of patients and 26.5% of patients had no prothrombotic risk factors (Table 1).

Table 1: Prothrombotic risk factors of patients

Prothrombotic risk factors	n	%
MTHFR mutation		42.85
C677T	7	
A1298C	8	
C677T+A1298C	2	
C677T+FVL	4	
FVL mutation	4	16.32
FVL+MTHFR(C677T)	4	
Elevated Lp(a)	4	8.16
Prothrombin G20210A mutation	2	4.08
PC deficiency	1	2.04

All patients' echocardiography results were normal. None had family histories of cerebrovascular disorders and stroke recurrence was not observed in any of the patients.

Patients had different presentations before receiving the diagnosis of PAIS. Around 59.1% presented with early handedness, 22.4% with seizures, 10.2% with hypotonia, 6.1% with apnea, 29.4% with hypotonia, and 2.2% with

encephalopathy. The epilepsy rate among patients was 73.3%, 6.4% of which had refractory epilepsy. All patients had different impairments in motor or cognitive functions. All the patients had unilateral cerebral palsy (UCP). Speech problems were present 34.2% of patients and 21.2% had behavioral problems.

On brain MRI investigations, 67.3% of patients had chronic encephalomalacia at frontotemporoparietal region supplied by the left middle cerebral artery, and 32.7% had chronic encephalomalacia at frontotemporoparietal region supplied by the right middle cerebral artery. Among all, 14.3% had cortical lesions.

Discussion

Perinatal arterial ischemic stroke is the most frequent type of pediatric stroke. It has been increasingly recognized with the availability and safe use of MRI in newborns in recent years. However, the etiopathogenesis of PAIS is not yet clear. PAIS has an extremely low recurrence rate, which suggests that pregnancy and perinatal state may have important roles in pathophysiology [10,11]. The majority of PAIS is most likely caused by thromboembolism passing from the placenta through the patent neonatal foramen ovale [12,13]. The left middle cerebral artery (MCA) is the most common vessel involved, with the left cerebral hemisphere being the most common region affected [14,15]. The emboli may pass through a patent foramen ovale or patent ductus arteriosus directly into the left common carotid artery and then to the left MCA [15]. Chorioamnionitis, congenital heart disease, twin pregnancy, bacterial meningitis, traumatic birth injury and peripartum asphyxia are the other main causes and risk factors of PAIS [6,12,15]. In accordance with the literature, peripartum asphyxia and twin pregnancy were the most common risk factors in our study.

Prothrombotic risk factors may be important causes of PAIS, and they were reported at different rates in previous studies. Kocaman et al. [8] stated that at least one of thrombophilia risk factors was present in 69% of the cases. Another study reported that thromboembolic risk factors were found in 68% of PAIS patients, compared with 24% of normal controls [17]. Curry et al. [18] found MTHFR mutations in 68% of PAIS patients. Kocaman et al. [8] reported that MTHFR mutation was the most frequent thrombophilic factor (57%), which was followed by FVL mutation (20%), like our study. In this study, 73.5% of patients had at least one of the prothrombotic risk factors.

PAIS may cause no or nonspecific symptoms, which may result in diagnostic delay. In the neonatal period, PAIS may present with focal and systemic symptoms including seizures, apnea, hypotonia, encephalopathy, feeding difficulties, fever, and irritability [19,20,21]. A delayed presentation after the age of 2 months was observed in 40% to 65% of PAIS in previous studies [19,21,22]. Presumed PAIS patients are generally referred to the pediatric neurology department because of handedness, seizure or neurodevelopmental delay. In this study, 50.9% of presumed PAIS patients presented with early handedness, 18.1% with seizure and 30% with neurodevelopmental delay.

PAIS is the one of the frequent causes of morbidity. Almost all PAIS patients present with UCP [23]. Children with PAIS who have cortical involvement carry a higher risk for epilepsy, cognitive impairment and learning disabilities [5,24]. Frequency of epilepsy is highly variable, ranging from 24.6% to 54%, among children with PAIS [24-27]. In this study, all patients presented with UCP and 73.3% had epilepsy, among which 6.4% had refractory epilepsy and all had cortical lesions on brain MRI. Speech problems were present 34.2% of patients and 21.2% had behavioral problems.

Limitation

The main limitation of this study is its retrospective nature. Additionally, there was no healthy control group in this study. To understand the role of prothrombotic risk factors in stroke mechanism, it would be more meaningful to compare the frequency of prothrombotic risk factors in PAIS patients with the healthy population.

Conclusion

PAIS is an important cause of neurologic and cognitive dysfunctions. However, the pathophysiology and causes of PAIS are not fully established. We determined that prothrombotic and maternal risk factors are important in the development of PAIS, in accordance with the literature. Risk factors' interdependence and role in the causal pathway of PAIS are still poorly understood. Multicenter prospective studies involving control groups are needed to determine the role of risk factors in the pathophysiology of PAIS.

References

1. Raju TN, Nelson KB, Ferriero D, Lynch JK; NICHD-NINDS Perinatal Stroke Workshop Participants. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics. 2007 Sep;120(3):609-16. doi: 10.1542/peds.2007-0336. PMID: 17766535.
2. Lee J, Croen LA, Lindan C, Nash KB, Yoshida CK, Ferriero DM, Barkovich AJ, Wu YW. Predictors of outcome in perinatal arterial stroke: a population-based study. Ann Neurol. 2005 Aug;58(2):303-8. doi: 10.1002/ana.20557. PMID: 16010659.
3. Lynch JK, Hirtz DG, DeVeber G, Nelson KB. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. Pediatrics. 2002 Jan;109(1):116-23. doi: 10.1542/peds.109.1.116. PMID: 11773550.
4. Grinnon ST, Miller K, Marler JR, Lu Y, Stout A, Odenkirchen J, Kunitz S. National Institute of Neurological Disorders and Stroke Common Data Element Project - approach and methods. Clin Trials. 2012 Jun;9(3):322-9. doi: 10.1177/1740774512438980. Epub 2012 Feb 27. PMID: 22371630; PMCID: PMC3513359.
5. Kirton A, Deveber G, Pontigon AM, Macgregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. Ann Neurol. 2008 Apr;63(4):436-43. doi: 10.1002/ana.21334. PMID: 18306227.
6. Li C, Miao JK, Xu Y, Hua YY, Ma Q, Zhou LL, Liu HJ, Chen QX. Prenatal, perinatal and neonatal risk factors for perinatal arterial ischaemic stroke: a systematic review and meta-analysis. Eur J Neurol. 2017 Aug;24(8):1006-1015. doi: 10.1111/ene.13337. Epub 2017 Jun 24. PMID: 28646492.
7. Sorg AL, von Kries R, Klemme M, Gerstl L, Weinberger R, Beyerlein A, Lack N, Felderhoff-Müser U, Dzietko M. Risk factors for perinatal arterial ischaemic stroke: a large case-control study. Dev Med Child Neurol. 2020 Apr;62(4):513-520. doi: 10.1111/dmcn.14347. Epub 2019 Sep 5. PMID: 31489622.
8. Kocaman C, Yilmaz Y. Etiological analysis of presumed perinatal stroke. Brain Dev. 2012 Feb;34(2):133-9. doi: 10.1016/j.braindev.2011.04.003. Epub 2011 May 11. PMID: 21561729.
9. Simchen MJ, Goldstein G, Lubetsky A, Strauss T, Schiff E, Kenet G. Factor v Leiden and antiphospholipid antibodies in either mothers or infants increase the risk for perinatal arterial ischemic stroke. Stroke. 2009 Jan;40(1):65-70. doi: 10.1161/STROKEAHA.108.527283. Epub 2008 Oct 16. PMID: 18927445.
10. Fluss J, Garcia-Tarodo S, Granier M, Villega F, Ferey S, Husson B, Kossorotoff M, Muehlethaler V, Lebon S, Chabrier S. Perinatal arterial ischemic stroke related to carotid artery occlusion. Eur J Paediatr Neurol. 2016 Jul;20(4):639-48. doi: 10.1016/j.ejpn.2016.03.003. Epub 2016 Mar 16. PMID: 27025300.
11. Dunbar M, Kirton A. Perinatal Stroke. Semin Pediatr Neurol. 2019 Dec;32:100767. doi: 10.1016/j.spen.2019.08.003. Epub 2019 Aug 7. PMID: 31813521.
12. Lehman LL, Beaute J, Kapur K, Danehy AR, Bernson-Leung ME, Malkin H, Rivkin MJ, Trenor CC 3rd. Workup for Perinatal Stroke Does Not Predict Recurrence. Stroke. 2017 Aug;48(8):2078-2083. doi: 10.1161/STROKEAHA.117.017356. Epub 2017 Jul 13. PMID: 28706112.
13. Fluss J, Dinomais M, Chabrier S. Perinatal stroke syndromes: Similarities and diversities in aetiology, outcome and management. Eur J Paediatr Neurol. 2019 May;23(3):368-383. doi: 10.1016/j.ejpn.2019.02.013. Epub 2019 Feb 27. PMID: 30879961.
14. Govaert P. Sonographic stroke templates. Semin Fetal Neonatal Med. 2009 Oct;14(5):284-98. doi: 10.1016/j.siny.2009.07.006. Epub 2009 Aug 13. PMID: 19682961.
15. Gunny RS, Lin D. Imaging of perinatal stroke. Magn Reson Imaging Clin N Am. 2012 Feb;20(1):1-33. doi: 10.1016/j.mric.2011.10.001. PMID: 22118590.
16. Wu YW, March WM, Croen LA, Grether JK, Escobar GJ, Newman TB. Perinatal stroke in children with motor impairment: a population-based study. Pediatrics. 2004 Sep;114(3):612-9. doi: 10.1542/peds.2004-0385. PMID: 15342829.
17. Günther G, Junker R, Sträter R, Schobess R, Kurnik K, Heller C, Kosch A, Nowak-Göttl U; Childhood Stroke Study Group. Symptomatic ischemic stroke in full-term neonates : role of acquired and genetic prothrombotic risk factors. Stroke. 2000 Oct;31(10):2437-41. doi: 10.1161/01.str.31.10.2437. Erratum in: Stroke 2001 Jan;32(1):279. PMID: 11022077.

18. Curry CJ, Bhullar S, Holmes J, Delozier CD, Roeder ER, Hutchison HT. Risk factors for perinatal arterial stroke: a study of 60 mother-child pairs. Pediatr Neurol. 2007 Aug;37(2):99-107. doi: 10.1016/j.pediatrneurol.2007.04.007. PMID: 17675024.
19. Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, Ferriero DM, Fullerton HJ, Barkovich AJ, Wu YW. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. JAMA. 2005 Feb 9;293(6):723-9. doi: 10.1001/jama.293.6.723. PMID: 15701914.
20. Chabrier S, Saliba E, Nguyen The Tich S, Charollais A, Varlet MN, Tardy B, Presles E, Renaud C, Allard D, Husson B, Landrieu P. Obstetrical and neonatal characteristics vary with birthweight in a cohort of 100 term newborns with symptomatic arterial ischemic stroke. Eur J Paediatr Neurol. 2010 May;14(3):206-13. doi: 10.1016/j.ejpn.2009.05.004. Epub 2009 Jun 21. PMID: 19541515.
21. Laugesaar R, Kolk A, Tomberg T, Metsvaht T, Lintrop M, Varendi H, Talvik T. Acutely and retrospectively diagnosed perinatal stroke: a population-based study. Stroke. 2007 Aug;38(8):2234-40. doi: 10.1161/STROKEAHA.107.483743. Epub 2007 Jun 21. PMID: 17585082.
22. Lee CC, Lin JJ, Lin KL, Lim WH, Hsu KH, Hsu JF, et al. Clinical Manifestations, Outcomes, and Etiologies of Perinatal Stroke in Taiwan: Comparisons between Ischemic, and Hemorrhagic Stroke Based on 10-year Experience in A Single Institute. Pediatr Neonatol. 2017 Jun;58(3):270-277. doi: 10.1016/j.pedneo.2016.07.005. Epub 2016 Nov 19. PMID: 28087259.
23. Nordstrand L, Eliasson AC, Holmefur M. Longitudinal development of hand function in children with unilateral spastic cerebral palsy aged 18 months to 12 years. Dev Med Child Neurol. 2016 Oct;58(10):1042-8. doi: 10.1111/dmcn.13106. Epub 2016 Mar 27. PMID: 27017925.
24. Bektaş G, Kipoğlu O, Pembegül Yıldız E, Aydınlı N, Çalışkan M, Özmen M, Sencer S. Epileptic spasm and other forms of epilepsy in presumed perinatal arterial ischemic stroke in Turkey after more than 10 years follow-up: A single centre study. Brain Dev. 2019 Sep;41(8):699-705. doi: 10.1016/j.braindev.2019.04.004. Epub 2019 Apr 16. PMID: 31003833.
25. Rattani A, Lim J, Mistry AM, Prablek MA, Roth SG, Jordan LC, Shannon CN, Naftel RP. Incidence of Epilepsy and Associated Risk Factors in Perinatal Ischemic Stroke Survivors. Pediatr Neurol. 2019 Jan;90:44-55. doi: 10.1016/j.pediatrneurol.2018.08.025. Epub 2018 Sep 21. PMID: 30409458.
26. Golomb MR, MacGregor DL, Domi T, Armstrong DC, McCrindle BW, Mayank S, deVeber GA. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. Ann Neurol. 2001 Aug;50(2):163-8. doi: 10.1002/ana.1078. PMID: 11506398.
27. Wanigasinghe J, Reid SM, Mackay MT, Reddihough DS, Harvey AS, Freeman JL. Epilepsy in hemiplegic cerebral palsy due to perinatal arterial ischaemic stroke. Dev Med Child Neurol. 2010 Nov;52(11):1021-7. doi: 10.1111/j.1469-8749.2010.03699.x. PMID: 20497457.

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