

Demographic and Clinical Features of Patients with Pediatric Stroke: A Cross-Sectional Study

Pediatric İnmeli Hastaların Demografik ve Klinik Özellikleri: Kesitsel Bir Çalışma

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ABSTRACT

Objective: In the pediatric age group, it is important to detect the risk factors of stroke and diagnose it early, and prevent the recurrence of the disease. This study aimed to conduct a descriptive analysis of demographic and clinical characteristics of pediatric stroke cases in the 0-18 age group and to evaluate the relationship between etiologic causes, risk factors and functional status of these cases.

Material and Methods: The medical files of the patients followed up by the Department of Pediatric Neurology of Ankara Training and Research Hospital were retrospectively examined. Cerebral magnetic resonance imaging and laboratory data were recorded. The Gross Motor Function Classification System, Box and Block Test, Nine-Hole Peg Test were used to evaluate the patients' current functional status.

Results: In 34 pediatric hemiplegic stroke cases, the median age of the onset of symptoms was one year (minimum 0, maximum 15 years). At the time of evaluation, hemiparesis was found in 73.5% of the cases and 41.2% had active seizures. Heterozygous factor V Leiden mutation was present in 17.6% of the patients, and homozygous MTHFR (c677c) mutation in 5.9%. When the etiologic factors were evaluated, there was a mass effect due to venous bleeding in 50%, arterial bleeding in 44.1%, and intracranial bleeding in 5.9% of the cases. Prophylaxis had been performed in 47.1% of the patients. There were no significant differences in functional parameters according to thrombophilic risk factors, whether the etiology was of arterial or venous origin, or whether they underwent prophylaxis ($p>.05$).

Conclusion: Half of the patients had a stroke of venous origin, and hemiparesis was present in approximately two-third of the cases. Functioning levels seemed to be independent of the presence of etiologic source or thrombophilic risk factors of the disease.

Key Words: Cerebral palsy, Hemiplegia, Pediatric age group, Stroke

ÖZ

Amaç: Çocukluk yaş grubunda inme risk faktörlerinin tespit edilerek erken teşhis edilmesi ve hastalığın tekrarının önlenmesi önemlidir. Bu çalışmada, 0-18 yaş grubundaki pediatrik inme olgularının demografik ve klinik özelliklerinin tanımlayıcı



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bir analizinin yapılması ve bu olguların etiyolojik nedenleri, risk faktörleri ve fonksiyonel durumları arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Ankara Eğitim ve Araştırma Hastanesi Çocuk Nörolojisi Bölümü tarafından takip edilen hastaların tıbbi dosyaları geriye dönük olarak incelendi. Serebral manyetik rezonans görüntüleme ve laboratuvar verileri kaydedildi. Hastaların mevcut fonksiyonel durumunu değerlendirmek için Kaba Motor Fonksiyon Sınıflandırma Sistemi, Kutu ve Blok Testi, Dokuz Delikli Peg Testi kullanıldı.

Bulgular: 34 pediatrik hemiplejik inme vakasında semptomların başlama yaşı ortanca bir yıldır (minimum 0, maksimum 15 yıl). Değerlendirme anında olguların % 73.5'inde hemiparezi bulundu ve % 41.2'inde aktif nöbet öyküsü vardı. Hastaların % 17.6'sında heterozigot faktör V Leiden mutasyonu, % 5.9'unda homozigot MTHFR (c677c) mutasyonu mevcuttu. Etiyolojik faktörler değerlendirildiğinde olguların % 50'sinde venöz kanamaya, % 44.1'inde arteriyel kanamaya ve % 5.9'unda intrakraniyal kanamaya bağlı kitle etkisi vardı. Hastaların % 47.1'ine profilaksi uygulanmıştı. Trombofilik risk faktörlerine göre, etiyolojinin arteriyel ya da venöz orijinli olmasına göre veya profilaksi uygulanıp uygulanmadığına göre fonksiyonel parametrelerde anlamlı farklılık yoktu ($p > .05$).

Sonuç: Hastaların yarısında venöz kaynaklı inme vardı ve vakaların yaklaşık üçte ikisinde hemiparezi mevcuttu. İşlevsel düzeyler, hastalığın etiyolojik kaynağı veya trombofilik risk faktörlerinin varlığından bağımsız görünüyordu.

Anahtar Sözcükler: Serebral palsy, Hemipleji, Pediatrik yaş grubu, İnme

INTRODUCTION

Pediatric stroke is an important cause of neurological morbidity in children. Sensorial and motor deficits, epilepsy, language problems, and behavioral problems can be seen in these children. Although the diagnosis and treatment guidelines are clearer in adults, there may be delays in diagnosis and treatment in pediatric cases due to the lack of clarity concerning childhood stroke (1, 2).

Cerebral palsy is a heterogeneous disease of the developing fetus or infant brain, which occurs due to non-progressive damage and affects movement and posture development. There are hemiplegic, diplegic and quadriplegic subtypes of the disease according to motor involvement (3). The most common cause of hemiplegic cerebral palsy is perinatal ischemic stroke. Pediatric strokes have been classified by age. Perinatal stroke is the name of a stroke that occurs between the 20th week of fetal life and 28th postnatal days as a result of the deterioration of cerebral blood flow due to arterial or venous thrombosis. Perinatal stroke has been classified as fetal, neonatal, and presumed (4). Presumed perinatal stroke symptoms are noticeable between 28 days and one year postnatally. The diagnosis of ischemic stroke is made retrospectively by the appearance of chronic infarction on neurological imaging (5). A stroke that develops between the 29th day and 18 years of life is considered as a childhood stroke (6).

Pediatric stroke can have hemorrhagic or ischemic origin with the latter being almost four times more frequent than the former (5). Ischemic strokes are further divided into the subtypes of arterial ischemic stroke and cerebral sinovenous thrombosis (7,8). The causes of pediatric stroke include arteriopathies, cardiac diseases, and thrombophilic factors. The most common cause of perinatal stroke is hypercoagulation. In addition to hypercoagulability, which is inherent in pregnancy, gene mutations, such as factor V Leiden and MTHFR may lead to the development of perinatal stroke (6). Although the causes and risk factors of pediatric stroke have been clearly defined in

the literature, the number of studies in the literature evaluating these risk factors and functional status is not sufficient. The current study aimed to evaluate the etiologic causes, risk factors, and functional status of patients with pediatric stroke.

MATERIALS and METHODS

The study was planned prospectively, and approval was obtained from the ethics committee of the tertiary care hospital. Written consent was obtained from the parents of all children who participated in the study. Patients who were followed up with the diagnosis of pediatric hemiplegia at the Department of Pediatric Neurology of Ankara Training and Research Hospital between June 2018 and 2019 were evaluated. The exclusion criteria were as follows: pain in the upper extremity, severe cognitive impairment, severe visual or auditory problems, history of upper extremity surgery, and a history of botulinum toxin injection into the upper extremity within the last six months.

Cerebral magnetic resonance imaging (MRI) and laboratory data showing the etiologic causes of the patients were retrospectively recorded. The systemic and neurological examinations of all cases were performed. The Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS), Box and Block Test (BBT), and Nine-Hole Peg Test (NHPT) were used to evaluate the patients' current functional status.

GMFCS: First developed for children with cerebral palsy, this system consists of five levels. **Level I:** Can walk without restriction. **Level II:** Can walk with restrictions without an assistive device. **Level III:** Can walk with assistive mobility devices, with restrictions walking outside home and in the community. **Level IV:** Self-movement is limited, children use powered mobility devices outside home and in the community. **Level V:** Extremely limited, even with the use of self-help assistive technology (9, 10). GMFCS can be applied to children between the ages of 0-18 years (11).

MACS: This system was developed for children with cerebral palsy to classify their ability to handle objects during their daily activities. It evaluates the participation of both hands in the activities together and cannot evaluate each hand individually. The description of the levels in this system is as follows: **Level I:** Handles objects easily and successfully. **Level II:** Handles most objects but with reduced quality or speed of achievement. **Level III:** Handles objects with difficulty; needs help to prepare or modify activities. **Level IV:** Handles a limited part of easily managed objects in adapted situations. **Level V:** Cannot handle objects and has severely limited ability to perform even simple actions. The validity and reliability of this system was previously investigated for children between four and 18 years, and the validity and reliability study of the Turkish version was undertaken by Akpınar et al. (12,13).

BBT: This test is used to evaluate the gross motor function of the upper extremity. It requires a 53.7 cm x 25.4 cm wooden box consisting of two sections, and 150 blocks with each edge being 2.5 cm. The patient is required to grasp the blocks one by one and pass them from one side of the box to the other. The number of blocks passed within one minute determines the score (14). This test can be used in children from three years of age (15).

NHPT: Developed to evaluate the fine motor function of the upper extremity and finger dexterity, this test involves the use of nine pegs with 9-mm width and 32-mm length and nine-hole test material appropriately sized for the pegs. The child is asked to place these pegs into the holes as quickly as possible, and this action is timed. This tool is used from age four. In this study, both BBT and NHPT were repeated three times, and the mean value was calculated. The tests were conducted using only one hand and applied for both upper extremities.

Statistical analysis:

SPSS v. 17.0 (Chicago Inc., 2008) was used for the statistical analyses. Categorical variables were expressed in frequency (n) and percentages (%), and continuous variables as a mean, standard deviation, median, minimum and maximum values. Normal distribution was evaluated by visual and statistical methods. Paired groups with normal distribution were analyzed using the independent samples t-test and those without normal distribution were analyzed by the Mann-Whitney U test. The chi-square and Fisher's exact tests were used for the analysis of categorical variables. The presence of correlations was assessed using the Spearman correlation test. Significance level was accepted as $p < 0.05$.

RESULTS

The study was completed with 34 pediatric hemiplegic stroke patients aged 0 to 18 years. The mean age at presentation was

Table 1: Demographic and clinical characteristics of pediatric hemiplegic stroke patients.

Variables	Outcome
Age at admission (years) ^a	10.2 ± 5.8 (0-18)
Age of onset of symptoms (years) ^b	1 (0-15)
Age at which rehabilitation started (years) ^b	2 (0.25-15)
Gender	
Male	23 (67.6)
Female	11 (32.4)
Presence of kinship between parents	
None	22 (64.7)
Second degree	8 (23.5)
Third and other degrees	4 (11.8)
Symptoms of admission	
Right hemiparesis	15 (44.1)
Seizures	7 (20.6)
Left hemiparesis	6 (17.6)
Loss of consciousness	3 (8.8)
Others	3 (8.8)
Presence of hemiparesis	
None	9 (26.5)
Yes	25 (73.5)
The presence of epilepsy-seizure	
None	20 (58.8)
Yes	14 (41.2)
Laboratory	
Factor 5 Leiden mutation	
Heterozygous	6 (17.6)
Negative	21 (61.8)
Not-applicable	7 (20.6)
MTHFR-c677c- mutation	
Homozygous	2 (5.9)
Heterozygous	10 (29.4)
Negative	15 (44.1)
Not-applicable	7 (20.6)
MTHFR-a1298c- mutation	
Heterozygous	11 (32.4)
Negative	15 (44.1)
Not-applicable	8 (23.5)
Etiological factors	
Venous	17 (50.0)
Arterial	15 (44.1)
Intracranial hemorrhage	2 (5.9)
Prophylaxis application	
None	18 (52.9)
Yes	16 (47.1)

a: Mean ± standard deviation (minimum – maximum), **b:** Median (minimum – maximum)

10.2 ± 5.8 years, and the median age of the onset of symptoms was one year (minimum 0, maximum 15 years). The median age at the time of the initiation of rehabilitation after diagnosis

Table II: Analysis of variables according to the presence of hemiparesis.

	Total (n=34)	Hemiparesis (n=25)	Not-hemiparesis (n=9)	p
Gender, *				
Male	23 (67.6)	18 (72.0)	5 (55.6)	.366
Female	11 (32.4)	7 (28.0)	4 (44.4)	
Epilepsy, *				
None	20 (58.8)	17 (68.0)	3 (33.3)	.116†
Yes	14 (41.2)	8 (32.0)	6 (66.7)	
Etiology, *				
Venous	17 (50.0)	11 (44.0)	6 (66.7)	.229‡
Arterial	15 (44.1)	13 (52.0)	2 (22.2)	
ICH	2 (5.9)	1 (4.0)	1 (11.1)	
Prophylaxis, *				
None	18 (52.9)	13 (52.0)	5 (55.6)	.855†
Yes	16 (47.1)	12 (48.0)	4 (44.4)	

*: n(%), †: Fisher's exact test, ‡: Analysis after controlling intracranial hemorrhage, **ICH**: Intracranial hemorrhage

Table III: Arterial versus venous origin of etiology and functional status parameters.

	Total (n=32)	Venous (n=17)	Arterial (n=15)	p
GMFCS, n (%)				
Level I	11 (34.4)	8 (47.1)	3 (20.0)	.138*
Level II	13 (40.6)	4 (23.5)	9 (60.0)	
Not applicable	8 (25.0)	5 (29.4)	3 (20.0)	
MACS, n (%)				
Aged under four	3 (9.4)	1 (5.9)	2 (13.3)	.221*
I	4 (12.5)	4 (23.5)	0	
II	3 (9.4)	1 (5.9)	2 (13.3)	
III	8 (25.0)	4 (23.5)	4 (26.7)	
IV	3 (9.4)	0	3 (20.0)	
V	3 (9.4)	2 (11.8)	1 (6.7)	
Not applicable	8 (25.0)	5 (29.4)	3 (20.0)	
BBT (box/min)	42.0 (14.5)	40.3 (14.4)	41.8 (15.3)	.825
NHPT (second)	41.5 (9.6)	42.1 (10.2)	40.1 (9.3)	.655

GMFCS: The Gross Motor Function Classification System, **MACS**: The Manual Ability Classification System, **BBT**: The Box and Block Test, **NHPT**: Nine-Hole Peg Test, *: Fisher's exact test

was two years (minimum 0.25, maximum 15 years). The clinical findings, laboratory data, etiologic factors, and prophylaxis rates of the patients are summarized in Table I.

In the analysis of the variables according to the presence of hemiparesis, no significant difference was found between the presence of hemiparesis and gender and epilepsy ($p > .05$) (Table II). In the analysis performed excluding two hemiplegic cases due to intracranial hemorrhage, no significant difference was observed between etiologic factors and motor functions when arterial and venous causes of stroke and functional status (GMFCS, MACS, BBT and NHPT scores) were compared ($p > .05$). Since three of the patients were under 4 years old, they were not evaluated with MACS (Table III). There was no significant difference in functional status according to whether the patients underwent prophylaxis ($p > .05$ for all variables, see Table IV).

No significant correlation was found between the age of the onset of symptoms and functional parameters (GMFCS, MACS, BBT and NHPT scores) except for the presence of a positive

correlation between the age of symptom onset and age at the initiation of rehabilitation (Spearman $\rho = .543$, $p = .024$). There was no significant difference in the GMFCS, MACS, BBT and NHPT scores according to the presence of thrombophilic causes [factor V Leiden mutation, MTHFR (c677c) mutation and MTHFR (a1298c) mutation] ($p > .05$).

When the patients were divided into two groups as perinatal stroke ($n = 18$, 53%) and childhood stroke ($n = 16$, 47%) and their results were compared, no significant difference was observed between the two groups in terms of the thrombophilic risk factors ($p > .05$). Although there was a difference between etiologic causes, no statistical significance was found (Table V). There was also no significant difference between the two groups concerning the symptoms at presentation ($p > .05$). Similarly, no significant difference was found in their functional status (GMFCS, MACS, BBT and NHPT scores) ($p > .05$). The incidence of hemiparesis was calculated as 77.8% ($n = 14$) in perinatal stroke cases and 75% ($n = 75$) in childhood stroke cases.

Table IV: Comparison of the functional status parameters of patients that underwent prophylaxis and those that did not receive this treatment.

	Total (n=32)	Prophylaxis (n=15)	Not-prophylaxis (n=17)	p
GMFCS, n (%)				
Level I	11 (34.4)	4 (26.7)	7 (41.2)	.671*
Level II	13 (40.6)	7 (46.7)	6 (35.3)	
Not applicable	8 (25.0)	4 (26.7)	4 (23.5)	
MACS, n (%)				
Aged under four	3 (9.4)	2 (13.3)	1 (5.9)	.284*
I	4 (12.5)	1 (6.7)	3 (17.6)	
II	3 (9.4)	0	3 (17.6)	
III	8 (25.0)	3 (20.0)	5 (29.4)	
IV	3 (9.4)	3 (20.0)	0	
V	3 (9.4)	2 (13.3)	1 (5.9)	
Not applicable	8 (25.0)	4 (26.7)	4 (23.5)	
BBT (box/min)	42.0 (14.5)	39.2 (14.5)	42.5 (10.5)	.624
NHPT (second)	41.5 (9.6)	39.7 (10.5)	42.1 (9.2)	.593

GMFCS: The Gross Motor Function Classification System, **MACS:** The Manual Ability Classification System, **BBT:** The Box and Block Test, **NHPT:** Nine-Hole Peg Test, *: Fisher's exact test

Table V: Comparison of the thrombophilic risk factors and etiological causes of perinatal stroke and childhood stroke patients.

	Perinatal stroke n = 18	Childhood stroke n = 16	p
Factor 5 Leiden*			0.38
Heterozygous	3 (16.7)	3 (18.8)	
Negative	14 (77.8)	7 (43.8)	
NA	1 (5.6)	6 (37.5)	
MTHFR-c677c*			0.39
Heterozygous	7 (38.9)	3 (18.8)	
Homozygous	1 (5.6)	1 (6.3)	
Negative	9 (50.0)	6 (37.5)	
NA	1 (5.6)	6 (37.5)	
MTHFR-a1298c*			0.59
Heterozygous	7 (38.9)	4 (25.0)	
Negative	10 (55.6)	5 (31.3)	
NA	1 (5.6)	7 (43.8)	
Etiology*			0.06
Arterial	11 (61.1)	4 (25.0)	
ICH	1 (0.5)	1 (6.2)	
Venous	6 (33.3)	11 (68.7)	

NA: not applicable, **ICH:** Intracranial hemorrhage, *: n(%)

DISCUSSION

In this study, the etiologic causes, risk factors and functional status of pediatric stroke patients were evaluated. It was concluded that venous or arterial origin or presence of thrombophilic causes did not have an effect on functional status. There was no difference between perinatal stroke and childhood stroke cases in terms of thrombophilic risk factors. Although there was no significant difference between the groups, arterial causes were the most common etiologic factors in perinatal stroke, whereas venous causes were higher in childhood stroke.

In a cohort study evaluating patients with perinatal stroke,

it was reported that perinatal arterial stroke was the most common cause (17). Golomb et al.(18) evaluated 22 patients with hemiparesis between two months and eight years of age and found arterial etiology in 22 patients. In another study that included 59 patients aged between 1.3 months and 77 months, arterial etiology was observed more frequently. While venous causes were etiologically determined in 12 patients, 47 patients had arterial etiology (5). In a more recent study, Kitau et al.(19) evaluated 156 patients with hemiplegic cerebral palsy and detected venous etiology at a rate of 60%. This higher rate of venous origin that was first reported in the literature was attributed by the authors to the genetic characteristics of the Japanese population. In the current study, arterial and venous causes were found to be etiologic factors of stroke at the

rates of 44% and 50%, respectively. In addition, perinatal and childhood stroke were evaluated separately for the first time, and those of arterial origin were seen more frequently (61%) in perinatal stroke cases similar to that found in the literature, whereas venous origin was found to be 68.7% in childhood stroke patients. No significant difference was found between the two groups, but this may be related to the sample size. This finding suggests that the frequency of venous etiologic causes may increase with age. Further studies with more patients can shed more light on this issue.

Prothrombotic factors are risk factors for pediatric stroke, and the literature indicates that they can be seen in 20-50% of these patients (6). In this study, a total of eight patients were found to have a prothrombotic risk factor, namely heterozygous factor V Leiden mutation in six and homozygous MTHFR-c677c-mutation in two cases. The overall rate of prothrombotic risk factors was 23.5%, which is consistent with the literature.

In the literature, hemiparesis has been reported in 55-61% of cases with childhood stroke (6,20). For perinatal stroke, this rate is around 58% (21, 22). In this study, the rate of hemiparesis was 77.8% for perinatal stroke and 75% for childhood stroke. Compared to the rate reported in the literature, the incidence of hemiparesis was slightly higher in the current study.

Kitai et al. (19) evaluated 156 children with hemiplegic cerebral palsy. Based on the MRI findings, they divided the patients according to the presence of arterial, venous and localized ischemic lesions and reported a difference at the intellectual level and in terms of epilepsy, but they found no difference in functional levels. It was concluded that epilepsy was more common in the presence of periventricular venous infarction. In our study, we observed that venous and arterial etiologic factors did not result in any difference in the functional status of patients. In addition, the presence of arterial or venous involvement did not affect the frequency of epilepsy.

In the literature, there are no studies investigating the relationship between functional status and prothrombotic factors. In our study, these risk factors were not associated with the presence of hemiparesis or that of epilepsy. There was also no significant difference in the functional status of cases with these risk factors.

There were some limitations of our study, with the most important being the small sample size. The reason for this was that the study was a single center study. We included all patients who were followed up and completed the inclusion criteria. This situation resulted in a further decrease in the number of patients when subgroup comparison was made. A reason for the lack of statistical difference in these subgroup analyzes may be the result of the small sample size. Multi-center studies may clarified on this situation. The second limitation concerns the cross-sectional design of the study, which may

not have allowed to sufficiently evaluate the effect of etiologic factors and risk factors on the functional status of patients. A prospective cohort study can explain the correlations between these parameters more clearly.

In conclusion, it can be stated that the presence of venous or arterial origin or the presence of thrombophilic causes has no effect on the functional status of pediatric stroke cases. While arterial causes are the most common etiologic factors in patients with perinatal stroke, venous causes are more common in childhood stroke.

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