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ORIGINAL RESEARCH

Epilepsy in Children with Down Syndrome: Case Series

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ABSTRACT

Epilepsy is more common in children with Down Syndrome than in the normal population. This study examined the clinical and treatment outcomes of children with epilepsy in Down syndrome. This study was conducted retrospectively in children with Down syndrome and epilepsy at the Child Neurology Clinic between January 2020 and August 2024. Medical records were examined in terms of gender, age, age at seizure onset, age at diagnosis, comorbidities, level of intellectual disability, seizure types, previously used antiepileptic drugs, antiepileptic drugs at the last follow-up, interictal electroencephalogram findings, and brain magnetic resonance imaging results. A total of twelve children (five boys and seven girls) with Down syndrome and epilepsy were identified. The median age of the patients was 105.5 months; the median age of seizure onset was twelve months. The seizure types of the patients were as follows: eight patients had focal seizures (focal clonic in six cases, focal tonic/clonic in two cases), three patients had epileptic spasms, and one patient had generalized seizures. When all antiepileptic drugs used by the patients were examined, it was seen that six patients used valproic acid, three patients used ACTH, three patients used phenobarbital, three patients used phenytoin, two patients used topiramate, and one patient used carbamazepine, lamotrigine, and levetiracetam. In this study, the frequency of epilepsy in individuals with Down Syndrome was determined to be 8.76%. Epilepsy in children with Down Syndrome can impede cognitive and motor development and significantly affect their quality of life, especially if diagnosis is delayed or therapeutic management is inadequate. Therefore, early diagnosis and correct treatment are essential for these patients.

Keywords: Down syndrome. Epilepsy. Child.

Down Sendromlu Çocuklarda Epilepsi: Olgu Serisi

ÖZET

Down Sendromlu çocuklarda epilepsi normal popülasyona göre daha yaygındır. Bu çalışmada Down sendromlu ve epilepsili çocukların klinik ve tedavi sonuçları incelendi. Bu çalışma Ocak 2020-Ağustos 2024 tarihleri arasında Çocuk Nöroloji Kliniği'nde Down sendromlu ve epilepsi tanısıyla izlenen çocuklarda retrospektif olarak yapıldı. Tıbbi kayıtlar cinsiyet, yaş, nöbet başlangıç yaşı, tanı yaşı, eşlik eden hastalıklar, zihinsel engellilik düzeyi, nöbet tipleri, daha önce kullanılan antiepileptik ilaçlar, son takipte kullanılan antiepileptik ilaçlar, nöbetler arası elektroensefalogram bulguları ve beyin manyetik rezonans görüntüleme sonuçları açısından incelendi. Down sendromlu ve epilepsili toplam oniki çocuk (beş erkek ve yedi kız) tespit edildi. Hastaların ortanca yaşı 105,5 ay, ortanca nöbet başlangıç yaşı oniki ay olarak bulundu. Hastaların nöbet tipleri şu şekildeydi; sekiz hastada fokal nöbetler (altı olguda fokal klonik, iki olguda fokal tonik/klonik), üç hastada epileptik spazmlar ve bir hastada jeneralize nöbetler mevcuttu. Hastaların kullandıkları tüm antiepileptik ilaçlar incelendiğinde altı hastanın valproik asit, üç hastanın ACTH, üç hastanın fenobarbital, üç hastanın fenitoin, iki hastanın topiramat, bir hastanın karbamazepin, lamotrijin ve levetirasetam kullandığı görüldü. Bu çalışmada Down Sendromlu bireylerde epilepsi sıklığının %8,76 olduğu saptanmıştır. Down Sendromlu çocuklarda epilepsi, bilişsel ve motor gelişimi engelleyebilir ve özellikle tanı gecikirse veya terapötik yönetim yetersizse yaşam kalitelerini önemli ölçüde etkileyebilir. Bu nedenle erken tanı ve doğru tedavi bu hastalar için çok önemlidir.

Anahtar Kelimeler: Down sendromu. Epilepsi. Çocuk.

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Down syndrome (DS) occurs in 1 in 700 to 1000 live births worldwide and is the most common cause of genetic intellectual disability.[1] It is caused by trisomy of all or part of chromosome 21 (47+21). Standard trisomy 21 is seen in approximately 95% of cases. Mosaic trisomy is seen in approximately 3–5% of DS cases. Robertsonian translocations are seen in approximately 4% of cases.[2] The mongoloid facial features, multiple congenital disabilities, intellectual disability, immune and endocrine dysfunction associated with DS result from this extra genetic material.[3] The seizure rates reported in DS range from 1 to 13%.[4] These rates are significantly higher than

those reported in the general population (0.35–1%). This highlights the importance of early evaluation and recognition of epilepsy in children with DS.[5] The higher seizure susceptibility in DS has been attributed to associated medical complications such as structural brain abnormalities, cardiovascular abnormalities, or recurrent infections.[4] A three-phase distribution of epilepsy has been described in Down syndrome, including infancy, early adulthood, and patients over 50 years of age. Epileptic spasms, which are late-onset and relatively benign in infancy, are the most common form. In the early adult group, focal seizures are the most common seizure type, while generalized seizures (including tonic-clonic seizures) are evenly distributed throughout life.[6] In this study, we examined the clinical and treatment outcomes of children with Down syndrome and epilepsy.

Material and Method

In this study, we reviewed retrospectively the medical records of patients diagnosed with Down syndrome and epilepsy at the Child Neurology Clinic between January 2020 and August 2024. During this period, a total of 25.612 examinations were performed, and 137 cases of Down syndrome were identified. Among these cases, 12 patients had comorbid epilepsy. In this study, we present data collected from 12 patients. Medical records were reviewed in terms of gender, age, age at seizure onset, age at diagnosis, comorbidities, level of intellectual disability, seizure types, previously used antiepileptic drugs, antiepileptic drugs at the last follow-up, follow-up period, interictal electroencephalogram (EEG) findings and brain magnetic resonance imaging (MRI) results. Seizure classification was based on clinical reports and EEG results. We divided epileptic seizures into the following 4 groups: (1) focal onset, (2) generalized onset, (3) epileptic spasms, and (4) seizures of unknown onset. EEG findings were classified into four groups: normal, hypsarrhythmia, epileptiform activity (spike/sharp waves), and background rhythm irregularity. The Stanford-Binet Intelligence Scales, Fifth Edition (SB-5), or the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V) were utilized to assess the level of intellectual disability in the patients. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a diagnosis of intellectual disability necessitates the presence of deficits in both intellectual functioning and adaptive functioning, with symptoms manifesting before the age of 22.[7] The study was conducted according to the Declaration of Helsinki. Since the study was designed retrospectively, written informed consent forms were not obtained from the patients. Data were analyzed using IBM SPSS statistics (version 28), and percentage, median, maximum, and minimum values were used in descriptive statistics.

Results

In this study, epilepsy was found in 12 of 137 cases of Down Syndrome. The frequency of epilepsy among individuals with Down Syndrome was determined to be 8.76%. The clinical and treatment results of twelve patients with DS and epilepsy are shown in of twelve children (five boys and seven girls) with DS and epilepsy were identified. Karyotype analysis revealed standard trisomy 21 in all individuals except one with chromosomal 9/21 translocation. The median age of the patients was 105.5 months (27-209), median age at seizure onset was 12 months (0.33-191), median age at diagnosis was 18 months (0.33-191), and median follow-up was 63 months (18-133). When the patients were examined in terms of comorbidities, nine patients (75%) had hypothyroidism, eight patients (66.7%) had congenital heart disease (six had severe congenital heart disease, two had secundum ASD), three patients (25%) had a history of stroke (one due to Moyamoya disease), and less commonly, one patient each had adrenal insufficiency, hearing loss, CD-19 deficiency, behavioral problems, Hirsprung disease, penoscrotal hypospadias, and Graves disease. Out of the nine patients diagnosed with hypothyroidism, seven were identified during the neonatal period. One patient was diagnosed at 13 months of age. Additionally, one patient developed drug-induced hypothyroidism at 3 years and 4 months. Six of the patients (50%) had moderate intellectual disability, three (25%) had mild intellectual disability, and three (25%) had severe intellectual disability. The seizure types of the patients were as follows: eight patients (66.7%) had focal seizures (six patients had focal clonic, two patients had focal tonic/clonic), three patients (25%) had epileptic spasms, and one patient (8.3%) had generalized seizures. When all antiepileptic drugs used by the patients were examined, six patients (50%) used valproic acid, three patients (25%) used ACTH, three patients (25%) used phenobarbital, three patients (25%) used phenytoin, two patients (16.7%) used topiramate, one patient (8.3%) used carbamazepine, lamotrigine, and levetiracetam. At the time of diagnosis, EEG findings were normal in four patients (33.3%), hypsarrhythmia in three patients (25%), epileptiform activity (two focal, one generalized) in three patients (25%), and background rhythm irregularity in two patients (16.7%). Brain MRI findings of the patients were normal in four patients (33.3%), chronic ischemic findings in three patients (25%), and, less frequently, hypoxic-ischemic encephalopathy findings, cerebral atrophy, mega cisterna magna, corpus callosum hypoplasia and colpocephaly and increased corpus

callosum thickness in one patient each (8.3%). At the last follow-up, all patients were seizure-free, and four patients had stopped their antiepileptic drugs. The drugs used by the patients at their previous follow-up are listed in Table I.

Discussion and Conclusion

This study presents the clinical and treatment results of 12 children with DS and epilepsy. The frequency of epilepsy among individuals with Down Syndrome was determined to be 8.76%. Most of our patients had standard trisomy 21 cases, and only one had a Robertsonian translocation. 58.3% of our patients were female and 41.7% were male. DS is the most common genetic cause of intellectual disability. It is seen in almost all patients. However, the degree of intellectual disability varies along a spectrum of severity.[8] In a study on intelligence scores in DS, 19% had an IQ of 50-69, 30% had an IQ of 35-49, 33% had an IQ of 20-34, and 18% had an IQ of less than 20.[9] Similarly, a study from Norway reported that the degree of intellectual disability in DS was 25% mild, 56% moderate, and 21% severe.[10] Consistent with the literature, 50% of our patients had moderate, 25% mild, and 25% severe intellectual disability.

Although DS has a variable phenotype, there are many common physical findings. These include hypotonia, epicanthic folds, flat nasal bridge, single palmar crease, and sandal toe gap. Children with DS have an increased risk of congenital anomalies, including congenital heart defects and abdominal wall abnormalities.[3] Individuals with DS are associated with both acquired and congenital thyroid disease. The incidence of congenital thyroid disease is significantly increased in infants with DS. One study estimated the incidence to be 26 times higher than the general population.[11] Infants born with DS are frequently diagnosed with congenital heart disease (54–66%) and have significant morbidity and mortality implications.[3] In this study, the most common comorbidities in our patients were hypothyroidism (congenital, acquired, or drug-induced) in 75%, severe congenital heart disease in 50%, and secundum ASD in 16.7%.

The prevalence of epilepsy, especially epileptic spasms, is increased in children with DS compared to the general population, ranging from 1% to 13%.[4] It has been hypothesized that genetic changes in ion channels and neurotransmitter function are secondary to increased susceptibility to seizures.[3] The most common seizure types in patients with DS include focal seizures (47%), epileptic spasms (32%), and generalized tonic-clonic seizures (21%).[8] In our study, seizure onset was before the age of 1 in half of our patients, and the most common seizure type was focal seizures (66.7%), and 25% of the patients had epileptic spasms.

The etiology of epilepsy in DS may be related to structural brain abnormalities, structural/metabolic disorders such as moyamoya disease, stroke, or complications of congenital cardiovascular abnormalities, such as hypoxic-ischemic encephalopathy. However, the underlying cause is unknown in many cases.[1] Normal MRI findings were detected in 33.3% of our cases. Brain MRI findings of the patients showed chronic ischemic findings in three patients and, more rarely, hypoxic-ischemic

Table I. Clinical Data on 12 Patients With Down Syndrome and Epilepsy.

Case	Sex	Age (M)	Karyotype	Comorbidity	Age at seizures onset (M)	Age at diagnosis (M)	Level of intellectual disability	Seizure types	Previously used AEDs	EEG	MRI	Outcomes and last AEDs
1	M	86	47,XY+21	Congenital hypothyroidism, Adrenocortical insufficiency, Behavioral problems	4	25	Moderate	Epileptic spasm	ACTH, VPA, VGB	Hypsarythmia	İncreased corpus callosum thickness	Seizure free, VPA, VGB
2	F	147	47,XX+21	Acquired hypothyroidism, Congenital heart disease, CD-19 deficiency	11	14	Moderate	Generalized myoclonic	VPA, LMT, TPM	Epileptiform activity (G)	Normal	Seizure free, VPA, TPM
3	M	27	47,XY+21	Congenital hypothyroidism, Congenital heart disease, Hearing loss	0.33	0.33	Mild	Focal clonic	FB	Normal	Corpus callosum hypoplasia, colpocephaly	Seizure free, FB
4	F	108	47,XX+21	Drug-induced hypothyroidism	25	25	Mild	Focal clonic	CBZ	Epileptiform activity (F)	Normal	Seizure free, AED-free
5	M	69	46,XY,rob(21;21)(q10,q10)+21	Congenital hypothyroidism, Congenital heart disease, Hirschsprung's disease	4	4	Severe	Focal tonic/clonic	DFH	Focal low frequency	Mega cisterna magna	Seizure free, AED-free
6	F	103	47,XX+21	Congenital hypothyroidism, Secundum ASD	9	10	Moderate	Epileptic spasm	ACTH, VPA	Hypsarythmia	Cerebral atrophy	Seizure free, AED-free
7	F	121	47,XX+21	Congenital hypothyroidism, Congenital heart disease	13	14	Severe	Epileptic spasm	ACTH, VPA, TPM	Hypsarythmia	Normal	Seizure free, VPA,TPM
8	M	50	47,XY+21	Secundum ASD, history of cerebral infarction	22	22	Moderate	Focal clonic	FB	Normal	Chronic ischemic findings	Seizure free,FB
9	F	209	47,XX+21	History of cerebral infarction, Moya moya disease, Graves disease	191	191	Moderate	Focal clonic	DFH	Normal	Chronic ischemic findings	Seizure free,DFH
10	M	33	47,XY+21	Penoscrotal hypospadias, Congenital heart disease, Hypoxic ischemic encephalopathy	6	6	Severe	Focal tonic/clonic	FB, DFH, LEV	Epileptiform activity (F)	Hypoxic ischemic encephalopathy	Seizure free,DFH, LEV
11	F	169	47,XY+21	Congenital hypothyroidism, History of cerebral infarction Tracheoesophageal fistula and esophageal atresia	124	124	Moderate	Focal clonic	VPA	Normal	Chronic ischemic findings	Seizure free,VPA
12	F	183	47,XY+21	Congenital hypothyroidism, Congenital heart disease	70	70	Mild	Focal tonic	VPA	Diffuse low frequency	Normal	Seizure free, AED-free

Abbreviations: M, male; F, female; M, month; AED, antiepileptic drug; ACTH, adrenocorticotropic hormone; VPA, valproic acid; VGB, vigabatrin; TPM, topiramate; FB, phenobarbital; CBZ, carbamazepine; DFH, diphenylhydantoin; LEV, levetriacetam; G, generalized; F, focal.

encephalopathy findings, cerebral atrophy, mega cisterna magna, corpus callosum hypoplasia, colpocephaly, and increased corpus callosum thickness in one patient each.

There are no pathognomonic EEG changes for DS. Most DS patients have normal EEG findings, especially in childhood and early adulthood, in the absence of seizures or severe neurodegeneration. Early pathological EEG changes are usually subtle and may present as a change in background EEG activity. As in individuals without DS, pathological EEG findings depend on the epilepsy and its syndromic classification.[2] EEG of our patients at the time of diagnosis was 33.3% normal, 25% hypsarrhythmia, and 25% epileptiform activity.

The principles of antiepileptic pharmacotherapy in DS patients do not differ significantly from those in diploid patients. There are no scientific studies on the possible superiority of individual antiepileptic drugs in epilepsy in patients with DS.[2] In general, epileptic spasms, when primarily symptomatic, are associated with a poor long-term prognosis. Consistent with a previous report[4], our patients had a better-than-expected response to treatment (mainly ACTH or VPA) and long-term seizure control. In the focal-onset group, seizures were also relatively well controlled (with different antiepileptic drugs). All our patients were seizure-free at the last follow-up, and antiepileptic treatments were discontinued in 33.3%.

The limitations of this study are that it was conducted on a small number of patients and was retrospective.

Epilepsy is a more common comorbidity in children with DS than in the normal population. In this study, the frequency of epilepsy in individuals with Down Syndrome was determined to be 8.76%. There are no pathognomonic EEG changes in DS. Pathological EEG findings depend on the epilepsy and its syndromic classification, as in individuals without DS. In general, epilepsy patients with Down syndrome respond well to traditional antiepileptic drugs. Epilepsy in children with DS can impede cognitive and motor development and significantly affect their quality of life, especially if the diagnosis is delayed or therapeutic management is inadequate. Therefore, early diagnosis and correct treatment are essential for these patients.

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