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Original Article

Investigation of Etiology, Treatment Outcomes and Risk Factors of Epilepsy in Down Syndrome

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ABSTRACT

Objective: Although epilepsy does not appear in the classic definitions of Down syndrome (DS), the prevalence of epilepsy is higher in these cases than in the general population. The purpose of this retrospective study was to evaluate the demographic, neuroradiological, and electrophysiological characteristics, and responses to treatment of patients with DS undergoing epileptic seizure.

Methods: Karyotype analysis, time of onset of seizures, types of seizure, electroencephalography (EEG) characteristic, antiepileptic drug used, and comorbidity were considered during evaluation. EEG and magnetic resonance imaging at the time of first admission were assessed during patient evaluation.

Results: Patients with DS (n=43) were enrolled in this study. Twenty-three of them were subjects with epilepsy. Seventeen (73.9%) of the 23 patients were boys and six (26.1%) were girls. The mean age of the patients was 21.7 months (standard deviation ± 4.8), and mean age at onset of seizures was 12.6 months. Comorbidity other than epilepsy was present in 13 (56.5%) patients. The most common seizure type, in 14 cases (60.9%), was focal seizures, four of which involved epilepsy developing following stroke secondary to cardiac surgery. Hypothyroidism was observed in all six patients with epileptic spasm. Only four of 20 patients without epilepsy have non-neurologic comorbidities.

Conclusion: This study may support the knowledge regarding the relationship between hypothyroidism and epilepsy in DS. Non-neurologic comorbidities are a significant risk factor for epilepsy in DS.

Keywords: Childhood, Down syndrome, epilepsy, epileptic spasm, hypothyroidism

INTRODUCTION

Down syndrome (DS) is the most common chromosomal disorder worldwide, affecting all races and genders. Most cases occur due to trisomy 21 through a non-disjunction mechanism. More rarely, it may be seen with balanced translocations or mosaicism. The reported prevalence in the USA is 12.6/10,000.[1] Children with DS have higher rates of heart disease, celiac disease, hypothyroidism, and epileptic disorders than the general population. Epilepsy is seen in 1.6-23.1% of children with DS, higher than general population.[2-10] Epilepsy in DS shows a bimodal distrubation, first in infancy and the second peak in the 6th decade.[11] The prevalence of epileptic spasm in these patients varies from study to study, from 6.7% to 66.7%.[3-12] Frequently seen predisposing factors are birth asphyxia, complex cardiac anomalies, history of major cardiac surgery, and stroke.

The first aim of this retrospective study was to evaluate the demographic, neuroradiological, and electrophysiological characteristics, and responses to treatment of patients with DS undergoing epileptic seizure. The second aim is to raise awareness in primary care physicians and podiatrists.

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MATERIALS AND METHODS

Seventy-two cases of DS presenting to our hospital for various reasons in 2019-2021 were included in the retrospective cross-sectional study. Twenty-three patients with histories of epilepsy and with resolved or new-onset epileptic seizures were investigated. Karyotype analysis, time of onset of seizures, types of seizure, electroencephalography (EEG) characteristics, antiepileptic drugs used, and comorbidities were considered during evaluation. The clinical, magnetic resonance, and electroencephalographic findings of patients diagnosed in our hospital were retrieved from the children's hospital records. The tests of cases with histories of epilepsy and treated in another center but followed up in our hospital were obtained from the data in the patients' possession. EEG and magnetic resonance imaging (MRI) at the time of first admission were assessed during patient evaluation. Patients with incomplete tests or who could not be contacted were excluded from the study.

Intractable epilepsy was defined as at least two seizures a month despite consecutive or concurrent use of two or more antiepileptics at appropriate dosages and durations.

The developmental status of the patients was evaluated by "Layton's Developmental Scale for Children with DS" until 72 months of age. After 72nd month gross motor function classification system was used.

Statistical Analysis

Data were processed through SPSS version 22.0. Quantitative variables were expressed as mean ± standard deviation (SD), and median range (maximum-minimum). Frequencies and percentages were calculated for all categorical characteristics. Chi-square analysis was used to compare dependent and independent variables. To compare the mean values, it was planned to use the Student t-test. Statistical significance was set at $p<0.05$.

The approval of the ethics committee has been obtained from Tekirdağ Namık Kemal University Non Invasive Clinical Research Ethics Committee (approval no: 2021.239.10.03, date: 26.10.2021).

RESULTS

Patients with DS (n=43) were enrolled in this study. Twenty-three of them were subjects with epilepsy. The patients' demographic, clinical, and laboratory findings are summarized in Tables 1 and 2.

In the epilepsy group, 17 (73.9%) of the 23 patients were boys and six (26.1%) were girls. The mean age of the patients were 21.7 months (minimum one, maximum 80, SD±4.8), and mean age at onset of seizures was 11.5 months. Comorbidity other than epilepsy was present in 14 (60.8%) patients. Four patients had undergone cardiac surgery, three for complete atrioventricular septal defect repair, and one for ventricular septal defect repair. The most common seizure type, in 14 cases (60.9%), was focal seizures, four of which involved epilepsy developing following stroke secondary to cardiac surgery. Seizures in five of the six patients with epileptic spasm ceased with adrenocorticotropic hormone (ACTH) therapy, while seizures in the other case were resistant, and vigabatrin therapy was added to treatment.

In the non-epileptic group, the mean age was 20.5 months (±2.5). Only four of 20 patients without epilepsy have non-neurologic comorbidities. One has cardiac malformation, 2 have hypothyroidism and one has celiac disease. In subjects with epilepsy, non-neurologic comorbidities were clearly increased and statistically significant ($p=0.01$).

DISCUSSION

Although epilepsy does not appear in the classic definitions of DS, the prevalence of epilepsy is higher in these cases than in the general population.[11-13] While focal seizures are generally seen, epileptic spasm is also observed at a higher rate than in the general population.[6-8] Although the seizure etiology varies, the most common factors are cardiovascular surgeries, previous infections, and structural cerebral abnormalities.[8] All comorbidities were more common in the group with epilepsy compared to the group without epilepsy ($p<0.01$). This finding reveals that the comorbidities are clearly the risk factor for developing epilepsy in DS.

The pathophysiology of epileptic spasms are still insufficiently understood. However, inhibitor and neurotransmitter imbalance has generally been implicated.[14] A difference in cortical laminar structures, and synaptic length and density has also been reported in children with DS compared to normal children, and seizures may cause a result.[15] Decreased oligodendrocyte myelination and differentiation and changes in action potential are also seen, and it has been suggested that these findings can result in intellectual disability and seizures in DS.[15]

Focal seizures were observed in six of the eight cases with cardiac anomalies in our patient group, generalized seizure in one, and epileptic spasm in one. One striking finding was the presence of hypothyroidism in all six children with epileptic spasms. This finding reveals that hypothyroidism may be a risk factor for epilepsy in patients with DS. Thyroid hormones play an essential role in the fetal brain development and physiological processes. Uncorrected hypothyroidism may cause epilepsy by effecting inhibitory neurotransmitters and inducing oxygen radicals.[16] The developmental stages of children without DS with congenital hypothyroidism determined at neonatal screening may be delayed compared to control group stages.[17] Even in case of regular L-thyroxine therapy in DS cases with early hypothyroidism, seizures are likely due to neuronal development being affected.

No such study considers antiepileptic drug tolerability and effectiveness in DS. Common rules for antiepileptic usage in childhood is valid in these patients. However, the comorbidites-like hypothyroidism or aggressive behavior- should always keep in mind. Generally, carbamazepine and levetiracetam in focal seizures, ACTH in epileptic spasms and valproate in myoclonic

Table 1. Comparison of demographic characteristics and laboratory findings of Down syndrome cases with and without epilepsy history

	Subjects with epileptic spasm	Subjects with other seizure types	Total (n=23)	Subjects without seizures (n=20)	p-value
Age (month)					
Mean (SD)	8.3 (±3.8)	22.6 (±4.61)	21.7 (±4.8)	20.5 (±2.5)	0.09
Gender					
Male n (%)	5 (21.7)	12 (52.2)	17 (73.9)	13 (65)	0.08
Female n (%)	1 (4.3)	5 (21.7)	6 (26.1)	7 (35)	0.1
Seizure onset					
<12 months n (%)	1 (4.3)	12 (52.1)	13 (56.5)	-	-
12 months-60 month n (%)	5 (21.7)	4 (17.3)	9 (39.1)	-	-
>60 months n (%)	-	1 (4.3)	1 (4.3)	-	-
Seizure onset (month)					
Mean (SD)	11 (±1.8)	13.2 (±2.81)	12.6 (±2.1)	-	-
Seizure type					
Epileptic spasm n (%)	6 (26.1)	-	6 (26.1)	-	-
Focal n (%)	-	14 (60)	14 (60.8)	-	-
Generalized n (%)	-	3 (13)	3 (13)	-	-
Electroencephalography					
Hypsarrhythmia n (%)	6 (26.1)	-	6 (26.1)	-	-
Focal epileptic activity n (%)	-	9 (39.1)	9 (39.1)	-	-
Generalized epileptic activity n (%)	-	3 (13)	3 (13)	-	-
Focal slow wave activity n (%)	-	5 (21.7)	5 (21.7)	-	-
Antiepileptic drug response at onset					
First drug n (%)	5 (21.7)	12 (52.1)	17 (73.9)	-	-
Add-on therapy n (%)	1 (4.3)	3 (13)	4 (17.3)	-	-
Intractable epilepsy n (%)	-	2 (8.6)	2 (8.6)	-	-
Magnetic resonance imaging					
Post-stroke gliosis n (%)	-	4 (17.3)	4 (17.3)	-	-
Cerebral atrophy and gliosis n (%)	1 (4.3)	2 (8.6)	3 (13)	-	-
Non-specific gliosis n (%)	1 (4.3)	4 (17.3)	5 (21.7)	-	-
Normal n (%)	4 (17.3)	7 (30.4)	11 (47.8)	-	-
Antiepileptic drug at last visit					
Monotherapy n (%)	6 (26.1)	7 (30.4)	13 (56.5)	-	-
Polytherapy n (%)	-	3 (13)	3 (13)	-	-
None n (%)	-	8 (34.7)	8 (34.7)	-	-
Non-neurologic co-morbidity					
Cardiopathy + hypothyroidism n (%)	1 (4.3)	2 (8.6)	3 (13)	-	-
Cardiopathy n (%)	-	5 (21.7)	5 (21.7)	1 (15)	0.01
Hypothyroidism n (%)	5 (21.7)	-	5 (21.7)	2 (15)	0.01
Chronic respiratory insufficiency n (%)	-	1 (4.3)	1 (4.3)	-	-
Celiac disease n (%)	-	-	-	1 (5)	
None n (%)	-	9 (39.1)	9 (39.1)	16 (65)	0.04
Total non-neurologic complications n (%)	6 (26)	8 (60.9)	14 (60.9)	4 (35)	0.01

SD: Standard deviation

Table 2. Demographics and clinical characteristics of all patients with epilepsy

Patients	Age (months)	Gender	Seizure onset (months)	Seizure type	EEG (initial)	MRI	AED response	Up-to-date AEDs	Comorbidity	Developmental status
1	12	Male	6	ES	Hypsarrhythmia	Normal	Partial response to ACTH, Vigabatrin added on.	The LEV	AVSD, Hypothyroidism	Had cardiac surgery, walks with aid, severe intellectual disability
2	18	Male	13	Focal	FEA	Post-stroke gliosis	Full response to the LEV.	None	VSD	Right hemiplegia walks independently, moderate intellectual disability
3	11	Female	5	Generalized	GEA	Normal	Full response to VPA.	None	None	Moderate intellectual disability
4	16	Male	12	ES	Hypsarrhythmia	Normal	Full response to ACTH.	The LEV	Hypothyroidism, ASD	Severe intellectual disability
5	12	Male	8	Generalized	GEA	Cerebral atrophy and gliosis	Partial response to the LEV.	LEV, CMZ	VSD	Spastic diplegia, cannot walk independently, mild intellectual disability
6	18	Female	12	ES	Hypsarrhythmia	Normal	Full response to ACTH.	The LEV	Hypothyroidism	Severe intellectual disability
7	15	Male	12	Focal	FEA	Post-stroke gliosis	Full response to CMZ.	CMZ	AVSD	Had cardiac surgery, right hemiplegia, walks with aid, mild intellectual disability
8	10	Male	5	Focal	FEA	Cerebral atrophy and gliosis	Partial response to the LEV.	The LEV, VPA, CMZ	ASD	Spastic tethraplegia, cannot walk, cortical blindness, mild intellectual disability
9	80	Male	72	Focal	Focal slowing	Normal	Full response to the LEV.	None	Hypothyroidism, ASD	Moderate intellectual disability
10	24	Female	18	Focal	FEA	Normal	Full response to PB.	None	VSD	Autism spectrum disorder, severe intellectual disability
11	12	Female	2	Focal	Focal slowing	Post-stroke gliosis	Partial response to the LEV.	The LEV, CMZ, CLB	VSD	Had cardiac surgery, right hemiplegia occurs and walk independently, mild intellectual disability
12	16	Male	13	ES	Hypsarrhythmia	Normal	Full response to ACTH.	The LEV	Hypothyroidism	Severe intellectual disability

Table 2. Demographics and clinical characteristics of all patients with epilepsy

Patients	Age (months)	Gender	Seizure onset (months)	Seizure type	EEG (initial)	MRI	AED response	Up-to-date AEDs	Comorbidity	Developmental status
13	11	Male	4	Focal	Focal slowing	Non-spesific gliosis	Full response to PB.	None	None	Mild intellectual disability
14	7	Male	5	Generalized	GEA	Normal	Full response to VPA.	None	None	Moderate intellectual disability
15	5	Male	2	Focal	Focal slowing	Non-spesific gliosis	Full response to the LEV.	The LEV	None	Mild intellectual disability
16	18	Male	12	ES	Hypsarrhythmia	Non-spesific gliosis	Full response to ACTH.	The LEV	Hypothyroidism	Severe mental retardation
17	10	Female	4	Focal	FEA	Post-stroke gliosis	Partial response to the LEV.	CMZ	AVSD, Chronic respiratory insufficiency	Had cardiac surgery, bedridden, trakeostomia, lower extremity spasticity, dependent to home-type mechanical ventilator, severe intellectual disability
18	12	Male	8	Focal	FEA	Non-spesific gliosis	Full response to the LEV.	The LEV	None	Moderate intellectual disability
19	15	Male	12	Focal	FEA	Normal	Full response to the LEV.	None	None	Moderate intellectual disability
20	12	Male	10	Focal	Focal slowing	Normal	Full response to the LEV.	The LEV	None	Mild intellectual disability
21	18	Male	11	ES	Hypsarrhythmia	Cerebral atrophy and gliosis	Full response to ACTH.	The LEV	Hypothyroidism	Severe intellectual disability and spastic tethraplegia
22	17	Male	10	Focal	FEA	Normal	Full response to the LEV.	None	None	Moderate intellectual disability
23	22	Female	10	Focal	FEA	Non-spesific gliosis	Partial response to CMZ.	The LEV	None	Moderate intellectual disability

ES: Epileptic spasms, EEG: Electroencephalography, FEA: Focal epileptic activity, GEA: Generalized epileptic activity, ACTH: Adrenocorticotropic hormone, the LEV: Levetiracetam, CMZ: Carbamazepine, CLB: Clobazam, VPA: Valproic acid, PB: Phenobarbital, AVSD: Atrioventricular septal defect, ASD: Atrial septal defect, VSD: Ventricular septal defect, AED: Antiepileptic drug, MRI: Magnetic resonance imaging

seizures should be the first choices.

Seizure control was achieved in 17 patients with the initial treatment initiated, while seizures were intractable in the remaining patients, and these patients used multiple antiepileptic therapies. Seizure control was established with intramuscular synthetic ACTH therapy in five of the six cases with epileptic spasms. The addition of vigabatrin being required in only one case. Previous studies have reported that epileptic spasm in cases of DS responds well to ACTH therapy.[8,9,18,19] One study even reported a response rate to ACTH of 98%.[20] Consistent with the previous literature, an ACTH response of approximately 83% was observed in cases with epileptic spasm-type seizures. However, other studies have suggested the exact opposite.[20,21] Nabbout et al.[22] reported five patients with DS diagnosed with infantile spasms. In this report epileptic spasms were stopped after short-term treatment with vigabatrin without any side effects. We attribute this literatural inconsistency to patient group heterogeneity and to differences in EEG interpretation. Cases with comorbidities such as cardiopathy and hypothyroidism were also included in our report.

Cardiac anomalies are observed at higher rates in cases with DS than in the general community and have been described as a risk factor for epileptic spasm in some studies.[19] In contrast to this hypothesis, cardiac anomalies were detected in only one of the six patients with epileptic spasms in this study. Patients with longer cardio-pulmonary bypass, aortic clamp times and deep hypothermic circulatory arrest also counted as risk factors for epilepsy after major cardiac surgery. Furthermore, extracorporeal membrane oxygenation use and longer hospital stays are also risk factors for stroke and post-cardiac operation epilepsy.[23]

Specific EEG pathologies were not seen, similar to previous studies.[11] Only the specific findings or commonly seen for the particular epileptic syndromes were revealed, such as hypsarrhytmia in epileptic spasms and focal discharges after post-stroke epilepsy.

Myoclonic seizures were not observed in the patient group. Comorbid late-onset myoclonic seizures and Alzheimer disease have been reported in cases of DS.[24] The absence of myoclonic seizures in the patient group may be because myoclonic seizures are usually seen in adults.

Developmental tests were applied to all patients. Before 72nd month "Layton's Developmental Scale for Children with DS" until 72 months of age.[25] After 72nd month gross motor function classification system was used. Mental problems were detected in all patients in spectrum from mild to severe intellectual disability. All patients without motor deficit have normal or non-spesific gliotic areas on the brain MRI. We can say that brain MRI can be predictive of motor deficits in the follow-up. All patients have some degree of intellectual disability as DS. All six patients with the history of infantile spasms have severe mental retardation in up-to-date examinations. This finding shows us the association between epilepsy type and intellectual functioning in this patient group.

Study Limitations

The current study had some limitations. First, the retrospective design may lead to the risk of bias. Second, the study was conducted in a single center with small sample size. However, the current study is one of the few studies, regarding the coexistence of DS and epilepsy, which was a rare condition. Studies are needed with a larger sample size of patients with DS and epilepsy.

CONCLUSION

This study may support the knowledge regarding the relationship between hypothyroidism and epilepsy in DS. Non-neurologic comorbidities are a significant risk factor for epilepsy in DS. Epilepsy in DS is not rare and should always be kept in mind by families, pediatricians, and family physicians.

Ethics

Ethics Committee Approval: The approval of the ethics committee has been obtained from Tekirdağ Namık Kemal University Non Invasive Clinical Research Ethics Committee (approval no: 2021.239.10.03).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.G., N.S., Concept: G.G., N.S., Design: G.G., N.S., Data Collection or Processing: G.G., Analysis or Interpretation: G.G., Literature Search: G.G., Writing: G.G., N.S.

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