INTERNATIONAL JOURNAL OF TECHNICAL AND NATURAL SCIENCES

DOI: https://doi.org//10.69648/WFAJ9917

International Journal of Natural and Technical Sciences (IJTNS), 2025; 5(2): 45-70

ijtns.ibupress.com

Online ISSN: 2671-3519

Application: 05.10.2025

Revision: 19.10.2025

Acceptance: 15.12.2025

Publication: 31.12.2025

Ademi, L. A., & Sukarova-Angelovska, E. (2025). Analysis of the electroencephalographic and clinical phenotype of epilepsy in children with small chromosomal changes. International Journal of Natural and Technical Sciences, 5(2), 45-68. https://doi.org//10.69648/WFAJ9917

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BALKAN JOURNALS

Analysis of the Electroencephalographic and Clinical Phenotype of Epilepsy in Children With Small Chromosomal Changes

Learta Alili Ademi, Elena Sukarova-Angelovska

Abstract

Background/aim: To determine the prevalence of epilepsy, the type of clinical presentation and the electroencephalographic characteristics of epilepsy in small chromosomal changes in a population of patients with epilepsy in the Republic of North Macedonia.

Materials and methods: This retrospective observational study included 193 patients, of which 101 patients with epilepsy (SV = 4.28, SD = 3.68, min 0.04 years, max 14 years) separated into two groups, group A with epilepsy and detected Copy number variations (CNVs); and B1 group with epilepsy where no CNVs were detected. The remaining 92 patients are with detected CNVs and without epilepsy, group B2. For comparing the groups and evaluating the qualitative data, Pearson chi-square test and Fisher's Exact Test were used to determine the degree of dependence between categorical variables with significance $p < 0.05$, using STATA 12.0 software package.

Results: The correlation between epilepsy and CNVs as two dependent variables is statistically strong (Cramer's V = - 0.5567) and significant Pr = 0.000. Pearson's chi2 = 59.8215, Fishers exact = 0.000. The occurrence of epilepsy in the subjects is independent of the type of CNVs.

Conclusion: The expansion of genetic research in recent years has shown that a large part of epilepsy has a genetic basis. Determining the electroclinical features of epilepsy in relation to the occurrence of small chromosomal changes may, in the future, provide a more appropriate classification of epilepsies and key information in identifying the role of genes involved in the development of epilepsy.

Keywords: Epilepsy, small chromosomal changes, epileptic seizures, EEG, CNVs

Introduction

Epilepsy, as a common neurological disorder affecting over 70 million people worldwide, 1-2% of children, is characterized by recurrent seizures (Fisher et al., 2014). A seizure is defined as a sudden alteration of behavior caused by intermittent changes in the electrical functioning of the brain. The expansion of genetic research and technologies in recent years has shown that a large part of unexplained epilepsies has a genetic basis (Hunter et al., 2022; Chen et al., 2017)

New studies indicate that in patients with epilepsy, where chromosomal changes are found, refractory epilepsy most often occurs. Despite the recent introduction of new antiepileptic drugs (AEDs), about 1/3 of patients with epilepsy have refractory epilepsy (Watson et al., 2014).

Refractory epilepsy, according to the International League Against Epilepsy (ILAE), is defined as failure to control seizures when using therapy with two appropriately selected and tolerated AEDs for an appropriate period of time (Fattorusso et al., 2021).

In many patients with small chromosomal changes, seizures occur either as typical or specific, or as nonspecific or refractory (Weise et al., 2012). They also have specific/typical characteristics in terms of EEG findings and response to AED (Pucci et al., 2008).

The latest classification of epilepsies according to ILAE 2017 is a multi-level classification, namely: first level (type of epileptic seizure), second level (type of epilepsy), third level (type of epileptic syndrome) (Scheffer et al., 2017; Hirsch et al., 2022; Specchio et al., 2022).

Copy number variations (CNVs) are defined as the duplication or loss of a portion of a DNA molecule (Battaglia et al., 2005). Many authors believe that submicroscopic CNVs (microdeletions, microduplications) are an important cause of epilepsy (Elia et al., 2001).

Studies show that 5-30% of patients with epilepsy have CNVs in the genome (Nagamani et al., 2013), and this is the case in about 3% of patients with idiopathic generalized epilepsy (IGE) and 1% of patients with focal epilepsies. This percentage is significantly higher when there is early-onset epilepsy in childhood, with alterations found in a large number of chromosomal regions, such as 14q12, 7q11.23, 15q13.3, 16p11.2, and 16p13.11 (Spreiz et al., 2014), 2q24.2-q24.3, 16p13.11-p13.2, 7q11.22, 15q11.2-q13.3 loci, as well as the 6q16.3q22.31 mi-

crodeletion (Szafranski et al., 2015). A European study involving 222 patients with epilepsy reported the detection of CNVs in 31.9% (Helbig et al., 2014), in 7.9% of 315 patients with epileptic encephalopathy (Mefford HC et al.,2011). In 1p36 deletion, epilepsy was reported in 68% of 86 patients (Verrotti et al., 2018; Greco et al., 2018). In a study of 87 patients with Wolf-Hirschhorn syndrome (del4p16.3), epilepsy was reported in 93%, of whom 81% had well-controlled epilepsy (Battaglia et al., 2009). The electroclinical phenotype of epilepsy in 15q13.3 microdeletion is characterized by absence seizures and focal EEG bursts (Whitney et al., 2021).

The main tool in the identification of genes for susceptibility to epilepsy is considered to be the analysis of electro-clinical features of epilepsy associated with CNVs. (Kurosawa et al., 2005)

Refractory epilepsy is common in Angelman syndrome, microdeletion 15q11-13, Prader-Willi syndrome, microdeletion 15q11.2-q13; 22q11.2 deletion (DiGeorge Syndrome), and 2p deletion. Rare cases of Williams syndrome (del7q11.23) have been reported to be associated with infantile spasms (Schinzel et al., 2001; Sorge et al., 2013).

Materials and Methods

In this retrospective nine-year observational study, the clinical and electroencephalographic characteristics of epilepsy, including the type of epilepsy, the specific EEG findings, and the response to AED in patients with small chromosomal changes, were analyzed. The above characteristics were compared with those of patients with epilepsy in whom CNVs were not detected. Data on clinical, genetic, and neurological examinations of 193 patients were collected from the files (hospital and/or outpatient) as well as the HIS system of the PHI University Clinic for Children's Diseases, in Skopje, including those from January 2015 to December 2023, in whom genetic analysis of array comparative genomic hybridization (arrayCGH) was performed.

This study was approved by the institutional ethics committee for human research of the Medical faculty, University St. Cyril and Methodius, in Skopje, North Macedonia, No 03-525/8, on February 7th 2024. The committee operates in accordance with the directive 2001/20/EC of the European Parliament and the Council since 04.04.2001. An informed consent form for participation in the study was prepared and signed by the parent, guardian, or legal representative of all participants prior to data inclusion in the study. The study was conducted in accordance with the

ethical principles of the Declaration of Helsinki and applicable national guidelines. Patient confidentiality was strictly maintained throughout the study.

The type of epilepsy, seizure types, and the response to AED are monitored in all subjects until the year 2023. All patients with CNVs and/or epilepsy, in whom aCGH was performed, were included. Inclusion and exclusion criteria include the following:

Inclusion criteria:

- Age of 0-14 years
- Diagnosis of epilepsy
- Diagnosis of microdeletions and/or microduplications

Exclusion criteria:

- Neurodegenerative diseases
- Cerebral palsy of non-genetic cause with no diagnosed epilepsy
- Neurological single gene disorders (e.g., neurofibromatosis, tuberous sclerosis)
- Known neurogenetic syndromes (Down syndrome and fragile X syndrome)

Based on the established diagnosis of epilepsy, a classification of epilepsy and seizures was performed. According to the 2017 ILAE Classification of Epilepsies, they were classified into focal and generalized epilepsy types. The type of seizure was determined due to hetero/anamnesis, classifying into focal with/without generalization and generalized according to the 2017 ILAE Classification of Seizures. The efficacy of the prescribed AED was also evaluated, and was classified into refractory (RE) and controlled epilepsy (CE) (2014 ILAE Definition).

EEG findings were re/evaluated for the diagnosis of epilepsy and determination of the type of epileptiform discharges. EEG findings were classified into generalized discharges, focal/multifocal discharges, hypsarrhythmia, and normal findings. Regarding the CNVs due to aCGH testing, microdeletion or/and/or microduplication was determined. Data on clinical characteristics were collected due to the presence/absence of dysmorphic features, motoric deficiency, and mental deficiency.

The results of neuroimaging analyses (brain MRI) were evaluated. For detection of the pathogenicity of the obtained changes, the aDGV (array Database of Genomic Variants) database was used, and other databases were included as needed – ClinVar, OMIM, Decipher, etc.

The following data were collected from the subjects: gender; age of first seizure; motor deficit; mental deficit, CNVs; type of EEG trace; type of epileptic seizure; types of epilepsy; dysmorphic features; changes in neuroimaging, number of AEDs used, and type of epilepsy in relation to refractoriness.

The classification of patients into groups was performed due to the presence/absence of epilepsy and/or the presence/absence of CNVs. Therefore, classified into: Group A (A) included those with epilepsy and CNVs, Group B1 (B1) with detected CNVs without epilepsy, and Group B2 (B2) with epilepsy without CNVs.

The classification of patients into groups is shown in Table 1.

Table 1:

Classification of patients into groups due to the presence/absence of epilepsy and/or the presence/absence of CNVs

Group A	**Group B**	
	B1	**B2**
Epilepsy and small chromosomal changes	CNVs without epilepsy	Epilepsy without CNVs

STATISTICAL ANALYSIS: Continuous data were interpreted using standard descriptive statistics: mean, standard deviation, maximum value, minimum value (SD; min-max), and number of observations. Categorical variables were summarized as absolute frequencies and percentages. Group comparisons were performed using Pearson's chi-square test to evaluate associations between categorical variables when expected cell counts were adequate. Fisher's exact test was applied in parallel for contingency tables with small cell counts to ensure the robustness of significance testing. Effect sizes were quantified using Cramér's V to complement *p*-values and to assess the magnitude of observed associations, with values >0.1 interpreted as clinically meaningful. A two-sided *p-value* <0.05 was considered statistically significant. All analyses were conducted using the STATA statistical software package (version 12.0), ensuring standardized and reproducible statistical evaluation of group differences.

Results

Genetic analysis (arrayCGH) was performed in 193 subjects. In 144 (74.6%) subjects, small chromosomal changes (CNVs) were detected, of which 69 (47.92%)

were female, and 75 (52.08%) were male. Of these, 84 (58.33%) had a microdeletion, 43 (29.86%) had a microduplication, while 17 (11.81%) had both a microdeletion and a microduplication. In the groups, microdeletion was the most common, detected in 30/52 (57.69%) of group A and in 54/92 (58.70%) of group B1. Microduplication was detected in 16/52 (30.77%) in Group A, and in 27/92 (29.35%) of Group B1 (as shown in Table 2). Microdeletions were the predominant CNV type in both groups. The distribution of CNV types between Group A and Group B1 did not differ significantly, as demonstrated by the chi-square test (p = 0.984), with a negligible effect size (Cramer's V = 0.015), indicating no meaningful association between CNV type and group allocation.

Table 2:

Analysis of the types of small chromosomal changes in each group of patients with CNVs (group A and group B1)

	Group A	Group B1	Total	Chi-square test	(P- value) *	Fisher's exact test	Cramers V
	N = 52	N = 92	N =144				
CNVs							
Microdeletion	30 (57.6%)	54 (58.7%)	84 (58.3%)	0.0331	0.984	1.000	0.0152
Microduplication	16 (30.8%)	27 (29.4%)	43 (29.9%				
Both	6 (11.5%)	11 (11.9%)	17 (11.8%)				

Statistical analysis was performed using STATA version 12.0. Statistical significance was assessed using the chi-square test ($p < 0.05$), with effect size estimated by Cramer's V (significant if > 0.1). Fisher's exact test was applied where appropriate.

Characteristics of the Patients

Out of 144 patients with small chromosomal changes, 108 (75%) had motor deficiency. Motor deficiency was present in 78/101 with epilepsy. Motor impairment was most frequently associated with microdeletions, occurring in 61 of 84 patients (72.6%), with a statistically significant association between CNV type and motor

deficit (Pearson's chi square (1) = 12.57, $p < 0.001$; Fisher's exact test $p < 0.001$), and a moderate effect size (Cramér's V = 0.35), indicating a meaningful relationship between microdeletions and motor dysfunction.

Mental deficit was noted in 133/144 subjects (92.36%) with small chromosomal changes, most prevalent in the microdeletion type of small chromosomal change, and in 79/84 (94.05%) subjects. However, due to the uniformly high prevalence, statistical discrimination between CNV types was limited, suggesting that mental deficit represents a core phenotype associated with CNVs irrespective of subtype.

Dysmorphia was noted in 137/144 (95.14%) of the patients with small chromosomal changes. In patients with epilepsy, it was noted in 87/101 (86.1%), group A = 49, group B2 = 38. However, no statistically significant association was found between epilepsy status and dysmorphia (Pearson's chi-square (1) = 0.16, p = 0.689; Fisher's exact test, $p = 0.776$; Cramér's V = 0.04), indicating a negligible effect size. (see Table 3 and Figure 1).

Table 3:

Analysis of demographic and clinical characteristics of patients in each group separately.

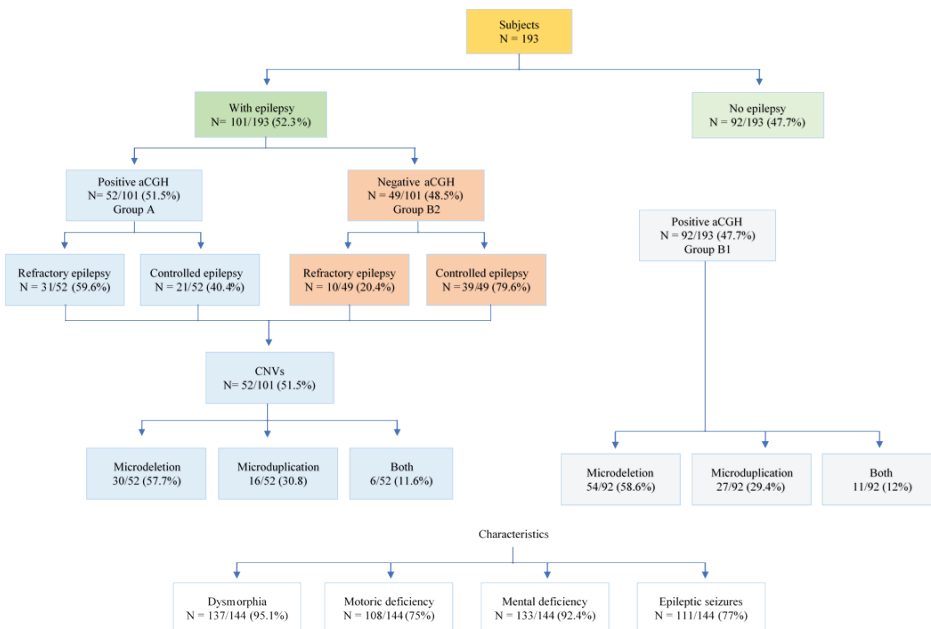
Statistical analysis using the statistical software package STATA 12.0, chi-square test, Fisher's exact test, and Cramer's V test were evaluated *significant at p<0.05, Cramer's V > 0.1

	Group A	Group B1	Group B2	Total	Chi square test	(P - value)*	Fishers exact test	Cramer's V
	N = 52	N = 92	N = 49	N =193				
Female	24 (46.2%)	45 (48.9%)	19 (38.8%)	88 (45.6%)	1.3335	0.513	0.538	0.0831
Male	28 (53.9%)	47 (51.1%)	30 (61.2%)	105 (54.4%)				
Dysmorphia	49 (94.2%)	88 (95.6%)	38 (77.6%)	175 (90.7%)	13.452	0.001**	0.003	0.2640
Motor deficit	48 (92.3%)	60 (65.2%)	30 (61.2%)	138 (71.5%)	15.370	0.000**	0.000	0.2822
Mental deficit	50 (96.2%)	83 (90.2%)	49 (100%)	182 (94.3%)	6.1477	0.046*	0.039	0.1785
*significant at 0.05 level, ** significant at 0.01 level								

When clinical characteristics were compared across all three groups (A, B1, and B2), significant differences were observed for dysmorphia (p = 0.001; Cramér's V = 0.26), motor deficit (p < 0.001; Cramér's V = 0.28), and mental deficit (p = 0.046; Cramér's V = 0.18), while sex distribution did not differ significantly between groups (p = 0.513). Demonstrated in Table 3. These findings support the presence of distinct clinical profiles across the patient groups.

Figure 1:

Graphical representation of the classification of patient groups and respondent clinical characteristics of patients in groups, and results of the survey analysis presented in percentage



Among patients with epilepsy, 39/60 (65%) were patients with the controlled type of epilepsy (group A = 18, group B2 = 21), while 39/41 (95.12%) were patients with the refractory type of epilepsy (group A = 30, group B2 = 9). Mental deficit was detected in controlled epilepsy 60/60 patients (group A = 21, group B2 = 39), while in refractory epilepsy 39/41 patients (group A = 29, group B2 = 10) (see Table 4). Despite these high prevalences, the association between epilepsy type (controlled vs. refractory) and clinical features did not reach statistical significance (Pearson's chi-square (1) = 2.99, p = 0.084; Fisher's exact test, p = 0.162), with a small-to-moderate effect size (Cramer's V = 0.17).

Table 4:

Prevalence of motor deficit, mental deficit, and dysmorphia in groups of patients with epilepsy (Group A and Group B2) in relation to types of epilepsy

Epilepsy type	**Motor deficiency**			
	Group A		Group B2	
	Absent (N)	Present (N)	Absent (N)	Present (N)
Refractory	1	30	1	9
Controlled	3	18	18	21
Total	4	48	19	30
Epilepsy type	**Mental deficiency**			
	Group A		Group B2	
	Absent (N)	Present (N)	Absent (N)	Present (N)
Refractory	2	29	0	10
Controlled	0	21	0	39
Total	2	50	0	49
Epilepsy type	Dysmorphia			
	Group A		Group B2	
	Absent(N)	Present (N)	Absent (N)	Present (N)
Refractory	2	29	3	7
Controlled	1	20	8	31
Total	3	49	11	38
N = number of patients				

Table 5:

Prevalence of epilepsy and types of epilepsy in patients with small chromosomal changes (group A + group B1).

*Statistical analysis using statistical software package STATA 12.0, chi square test, Fishers exact test and Cramers V test were evaluated *significant at p<0.05, Cramers V > 0.1*

CNVs	**Epilepsy**		**Total**
	No	Yes	
None	0	49 (48.5%)1	49 (25.39%)
Present	92 (100.00%)	52 (51.49%)	144 (74.61%)
Total	**92 (**100.00%)	**101 (**100.00%)	**193 (**100.00%)
Pearson's chi2(1) = 59.8215 Pr = 0.000, Cramer's V = - 0.5567, Fishers exact = 0.000			

CNVs	Epilepsy type		Total
	Refractory	Controlled	
None	10 (9.90%)	39 (38.61%)	49 (48.51%)
Present	31 (30.69%)	21 (20.79%)	52 (51.49%)
Total	41 (40.59%)	60(59.41%)	101
Pearson's chi2(1) = 16.0812 Pr = 0.000, Cramer's V = 0.3990, Fishers exact = 0.000			

Epilepsy was diagnosed in 101 of the patients, of which 43/101 (42.57%) were female, 24 (55.8%) from group A and 19 (44.2%) from group B2, while 58/101 (57.43%) were male, Group A = 28 (48.2%) and Group B2 = 30 (51.8%) (see Table 5). N = 41 (40.59%) had refractory epilepsy, of whom 19 (46.34%) were female, and 22 (53.66%) were male, while N = 60 (59.41%) had controlled epilepsy, of whom 24 were female (40%) and 36 were male (60%) (see Table 5). Sex distribution did not show a marked imbalance between refractory and controlled epilepsy, suggesting that sex was not a major determinant of epilepsy severity in this cohort.

A highly significant association was observed between the presence of CNVs and epilepsy (Pearson's chi-square (1) = 59.82, $p < 0.001$; Fisher's exact test, $p < 0.001$). All patients without CNVs were non-epileptic, whereas epilepsy was present in 52 of 144 patients (51.5%) with CNVs. The effect size was large (Cramer's V = 0.56), indicating a strong and clinically meaningful association between CNVs and the occurrence of epilepsy.

Furthermore, CNV status was significantly associated with epilepsy type (refractory versus controlled) (Pearson's chi-square (1) = 16.08, $p < 0.001$; Fisher's exact test, $p < 0.001$). Refractory epilepsy was more frequent among patients with CNVs (31/52, 59.6%) compared with those without CNVs (10/49, 20.4%), whereas controlled epilepsy predominated in patients without CNVs. The corresponding Cramer's V value (0.40) indicates a moderate-to-strong effect size, suggesting that the presence of CNVs is not only associated with epilepsy occurrence but also with increased epilepsy severity. Overall, Table 5 demonstrates a robust statistical relationship between small chromosomal changes and both the presence and refractoriness of epilepsy, supported by highly significant *p*-values and moderate-to-large effect sizes, underscoring the clinical relevance of CNVs in epilepsy risk stratification.

Neuroimaging was performed in 135/193 of patients from the groups, namely group A = 52, group B1 = 60, and group B2 = 49. The most common finding was normal findings, in 83 patients, compared to 52 patients with abnormalities in

brain structures. When neuroimaging findings were compared across Groups A, B1, and B2, normal imaging remained the predominant finding in all groups. Statistical comparison did not demonstrate a significant difference in the distribution of normal versus abnormal neuroimaging findings between groups (chi-square test, $p > 0.05$), indicating that the presence of structural brain abnormalities was not strongly associated with group allocation.

Clinical Characteristics of Epileptic Seizures and Epilepsy

Epileptic seizures were detected in a total of 107 patients, i.e., in 101 patients with epilepsy, group A = 52, group B1 = 6, and group B2 = 49, of which the generalized type occurs in a total of 50/107 patients, namely in 25/52 subjects from group A, 2/92 patients from group B1 and 23/49 patients from group B2. In group A, the most common type of epileptic seizure is generalized, in group B1, the most common type of epileptic seizure is focal (4/6), while in group B2, the most common type of epileptic seizure is focal with/without generalization (26/49). Due to the small number of epileptic patients in Group B1, statistical comparisons of seizure types were performed between Group A (patients with CNVs) and Group B2 (patients without CNVs) (see Table 6).

As shown in Table 6, seizure-type distribution differed significantly between Groups A and B2 when stratified by epilepsy type (refractory vs. controlled). The overall comparison demonstrated a statistically significant association between seizure type and group allocation (Pearson's chi-square (2) = 27.83, $p < 0.001$; Fisher's exact test, $p < 0.001$), with a large effect size (Cramer's V = 0.53), indicating a strong and clinically meaningful relationship.

In patients with refractory epilepsy, polymorphic seizures were the most common seizure type, occurring in 26 of 41 patients (63.4%), including 18 patients from Group A and 8 patients from Group B2. Conversely, in patients with controlled epilepsy, generalized seizures predominated, affecting 36 of 60 patients (60.0%), with 15 patients from Group A and 21 patients from Group B2 (see Table 6).

Table 6:

Analysis of seizure types in types of epilepsy in patients with (group A) and without CNVs (group B2) using the statistical software package STATA 12.0.

*Statistical analysis using the statistical software package STATA 12.0, chi-square test, Fisher's exact test, and Cramér's V test were evaluated *significant at p<0.05, Cramér's V > 0.1*

Epileptic seizure type	Group A		Group B2		
	Refractory epilepsy	Controlled epilepsy	Refractory epilepsy	Controlled epilepsy	Total
Focal with/without generalization	3 (9.7%)	4 (19.1%)	0	12 (30.7%)	19
Generalized	10 (32.3%)	15 (71.4%)	2 (20%)	21 (53.9%)	48
Polymorphic	18 (58%)	2 (9.5%)	8 (80%)	6 (15.4%)	34
Total	31	21	10	39	101
(Pearson chi2 (2) = 27.8349. Pr = 0.000, Cramer's V = 0.5250, Fishers exact = 0.000).					

Polymorphic seizures were strongly associated with refractory epilepsy, especially in patients with CNVs, suggesting a more complex and severe epileptic phenotype in this group. In contrast, generalized seizures were more common in controlled epilepsy, regardless of CNV status, indicating a comparatively more favorable seizure profile. Overall, these findings indicate that seizure semiology differs between patients with and without CNVs and between refractory and controlled epilepsy, with CNV-positive patients showing a higher burden of complex and polymorphic seizure types.

The age of onset of the first seizure in the subjects is equally distributed under 1 year of age and over 1 year of age. In 52/107 (48.6%) subjects with epileptic seizures, the first seizure occurred under 1 year of age, while in 55/107 (51.4%) subjects, it occurred over 1 year of age. However, group-wise analysis revealed a significant difference in the timing of seizure onset. In Group A, seizure onset most frequently occurred before 1 year of age, affecting 32 of 52 patients (61.5%), whereas in Group B2, seizure onset was more commonly observed after 1 year of age, occurring in 31 of 49 patients (63.3%). Statistical analysis demonstrated a significant association between group allocation and age at seizure onset (Pearson's chi-square (2) = 6.81, p = 0.033; Fisher's exact test, p = 0.038). Furthermore, the Cramer's V value exceeding 0.1 (Cramer's V = 0.25) indicates that the association is not only statistically significant but also of potential clinical relevance, suggesting that CNV-positive epilepsy is associated with an earlier onset of seizures.

Regarding antiepileptic therapy, the most common is the use of monotherapy, in 59 subjects, while polytherapy is used in 42 subjects. However, in group A, polytherapy with AED is used in most subjects, in 28 subjects, compared to group B2, in which polytherapy is used in 14 subjects. Statistical analysis demonstrated a significant association between group allocation and AED treatment strategy (Pearson's chi-square = 6.63, p = 0.010; Fisher's exact test, p = 0.009–0.015). The effect size was small to moderate (Cramer's V = 0.26), indicating a clinically relevant difference in treatment complexity between groups. Although monotherapy predominated in the overall cohort, patients in Group A were significantly more likely to require AED polytherapy than patients in Group B2. The statistically significant p-values confirm that this difference is unlikely to be due to chance, while the Cramer's V value exceeding 0.1 indicates a meaningful association. These findings suggest that patients in Group A exhibit a more severe or treatment-resistant epilepsy phenotype, necessitating more complex pharmacological management.

Among the 101 patients diagnosed with epilepsy, generalized epilepsy was the most frequent epilepsy type, occurring in 57 patients (56.4%). Generalized epilepsy was more common in Group A, affecting 33 of 52 patients (63.5%), compared with Group B2, where it was observed in 24 of 49 patients (49.0%). Focal epilepsy with or without secondary generalization was identified in 32 patients (31.7%), with a higher prevalence in Group B2 (22 patients) than in Group A (10 patients). Epileptic encephalopathies were less frequent: West syndrome was diagnosed in 11 patients (10.9%), while Dravet syndrome was observed in only one patient (1.0%). Statistical analysis demonstrated a significant association between epilepsy type and group allocation (Pearson's chi-square (3) = 9.11, p = 0.028; Fisher's exact test p = 0.019), with a moderate effect size (Cramer's V = 0.30), indicating that epilepsy classification differed meaningfully between patients with and without CNVs.

Within the CNV-positive group (Group A), generalized epilepsy was most commonly associated with microdeletions (15/33), followed by microduplications (14/33) and combined CNVs (4/33). Focal epilepsy was less frequent and was observed across all CNV subtypes. West syndrome was identified predominantly in patients with microdeletions. However, the overall association between CNV subtype and epilepsy type did not reach statistical significance (Pearson's chi-square (6) = 9.93, p = 0.128; Fisher's exact test, p = 0.080), despite a moderate effect size (Cramer's V = 0.31). More detailed analysis of types of epilepsy due to types of small chromosomal changes is shown in Table 7.

Table 7:

Analysis of prevalence of the type of epilepsy in relation to the type of small chromosomal change in patients with CNVs (group A)

*Statistical analysis using the statistical software package STATA 12.0, chi-square test, Fisher's exact test, and Cramér's V test were evaluated *significant at p<0.05, Cramér's V > 0.1*

CNVs type	Focal	Generalized	Dravet sy	West sy	Total
Microdeletion	6 (60.00%)	15 (45.45%)	1 (100.00%)	8 (10.00%)	30 (57.69%)
Microduplication	2 (20.00%)	14 (42.42%)	0 (0.00%)	0 (0.00%)	16 (30.77%)
Both	2 (20.00%)	4 (12.12%)	0 (0.00%)	0 (0.00%)	6 (11.54%)
Total	10 (100.00%)	33 (100.00%)	1 (100.00%)	8 (100.00%)	52 (100.00%)
Pearson chi2 (6) = 9.9299. Pr = 0.128, Cramer's V = 0.3090, Fishers exact = 0.080					

Regarding epilepsy severity, refractory epilepsy was markedly more prevalent in Group A, affecting 31 of 41 patients with refractory epilepsy (75.6%), compared with 10 of 41 patients (24.4%) in Group B2, indicating a strong association between CNV presence and treatment-resistant epilepsy. Overall, statistically significant findings support the conclusion that CNV status is associated with both epilepsy type and severity. Within Group A, refractory epilepsy was more common than controlled epilepsy (31/52, 59.6% vs. 21/52, 40.4%), indicating a higher burden of treatment-resistant epilepsy among patients with CNVs.

Electroencephalographic Characteristics

Electroencephalography (EEG) was performed in 74/144 subjects with small chromosomal changes, of which focal/multifocal epileptiform seizures were noted in 33/73 (44.59%) subjects (group A = 20, group B1 = 13), generalized seizures in 27/73 (36.49%) subjects (group A = 22, group B1 = 5). Statistical analysis demonstrated a significant difference in EEG epileptiform patterns between groups (Pearson's chi-square (6) = 13.01, p = 0.043; Fisher's exact test p = 0.045), with a moderate effect size (Cramer's V = 0.30), indicating a meaningful association between group allocation and EEG seizure pattern (see Table 8).

The most common EEG finding in the groups is focal/multifocal bursts in 63/123 subjects; however, in group A, the most common finding is generalized bursts in 22 subjects. Hypsarrhythmia occurred in 9 (12.16%) subjects (9 from group A), while normal findings were noted in 5 patients. The distribution of EEG findings differed significantly among the three groups (Pearson's chi-square (6) = 23.91, p = 0.001; Fisher's exact test, *p* = 0.002), with a moderate effect size (Cramer's V = 0.31). These results indicate that EEG patterns vary significantly according to group, with more severe and generalized EEG abnormalities, including hypsarrhythmia, clustering in patients with CNVs, particularly in Group A (Table 8).

Table 8:

Analysis of clinical and electroencephalographic characteristics of epilepsy in each group of patients (group A, group B1, and group B2).

*Statistical analysis using the statistical software package STATA 12.0, chi-square test, Fisher's exact test, and Cramer's V test were evaluated *significant at p<0.05, Cramer's V > 0.1*

N = 52		Group A	Group B1	Group B2	Total	Chi square test	(P - value) *	Fisher`s exact test	Cramer's V
	N = 92	N = 49	N =193						
Epilepsy		52		49	101				
Type						16.0812	0.000**	0.000	0.3990
Refractory		31 (59.62%)		10 (20.41%)	41 (40.59%)				
Controlled		21 (40.38%)		39 (79.59%)	60 (59.41%)				
Type						9.1127	0.028*	0.019	0.3004
Focal		10 (19.23%)		22 (44.90%)	32 (31.68%)				
Generalized		33 (63.46%)		24 (48.98%)	57 (56.44%)				
Dravet sy		1 (1.92%)			1 (0.99%				
West sy		8 (15.38%)		3 (6.12%)	11 (10.89%)				

Epileptic seizure	52	6	49	107	10.5087	0.033*	0.048	0.2216
Focal	7 (13.46%)	4 (66.67%)	12 (24.49%)	23 (21.5%)				
Generalized	25 (48.08%)	2 (33.33%)	23 (46.94%)	50 (46.73%)				
Polymorphic	20 (38.46%)		14 (28.57%)	34 (31.78%)				
EEG findings	52	21	49	122	23.9085	0.001**	0.002	0.3118
Focal/multifocal	20 (38.46%)	13 (59.09%)	30 (61.22%)	63 (51.22%)				
Generalized	22 (42.31%)	5 (22.73%)	16 (32.65%)	43 (34.96%)				
Hypsarrhythmia	9 (17.31%)		3 (6.12%)	12 (9.76%)				
Normal	1 (1.92%)	4 (18.18%)		5 (4.07%)				
Neuroimaging	52	60	49	161	0.8957	0.639	0.650	0.0746
Normal	32 (61.54%)	42 (70%)	32 (65.31%)	106 (65.84%)				
Abnormal	20 (38.46%)	18 (30%)	17 (34.69%)	55 (34.16%)				
AET	52		49	101	6.6343	0.010**	0.015	-0.2563
Monotherapy	24 (46.15%)		35 (71.43%)	59 (58.42%)				
Polytherapy	28 (53.85%)		14 (28.57%)	42 (41.58%)				
Age of first seizure					6.8061	0.033*	0.038	0.2522
< 1 year old	32 (61.54%)	2 (33.33%)	18 (36.73%)	52 (48.60%)				
>1year old	20 (38.46%)	4 (66.67%)	31 (63.27%)	55 (51.40%)				
*significant at 0.05 level, ** significant at 0.01 level								

Electroclinical Characteristics of Small Chromosomal Changes

The most common type of epileptic seizure in subjects with small chromosomal changes is a generalized epileptic seizure, which occurs in 27 subjects out of a total of 58 subjects who experienced an epileptic seizure (see Table 8). Epileptic seizures most often occur in a microdeletion type of chromosomal change, in 33/58 (56.90%) subjects. Statistical analysis did not demonstrate a significant association between seizure type and CNV subtype (microdeletion, microduplication, or combined changes) (Pearson's chi-square (4) = 5.06, p = 0.281; Fisher's exact test, p = 0.23). The effect size was small to moderate (Cramer's V = 0.21), suggesting a possible trend without reaching statistical significance, likely influenced by the limited sample size within CNV subgroups.

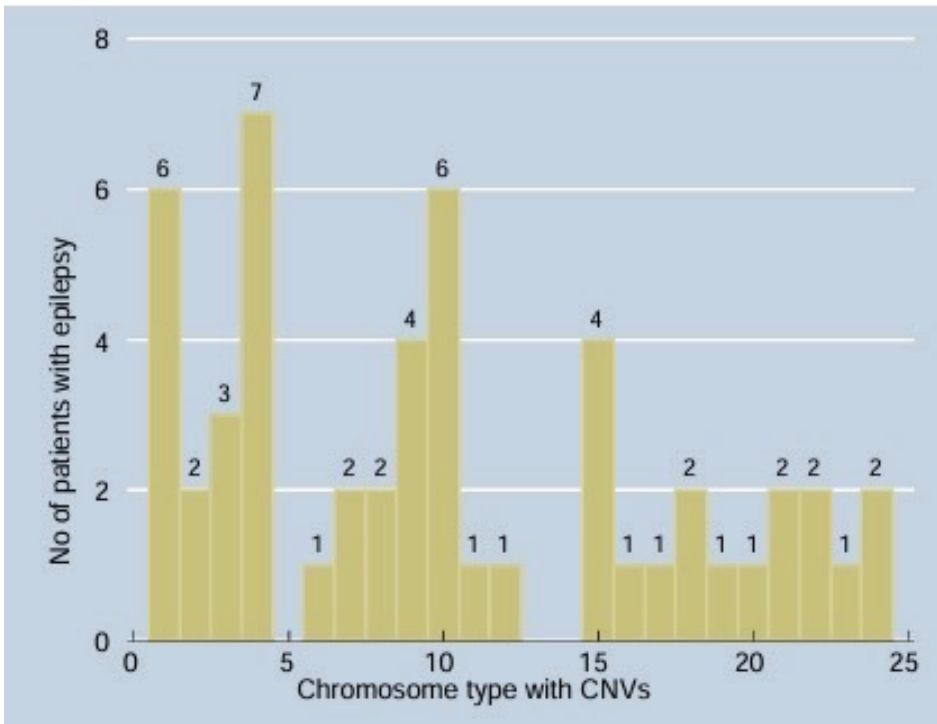
Although generalized seizures and microdeletions predominated among patients with CNVs and epilepsy, the lack of statistical significance indicates that seizure type is not strongly determined by CNV subtype alone. The modest effect size suggests a potential association that may become evident in larger cohorts.

The largest number of subjects with epilepsy were noted in small chromosomal changes on chromosome 4. Also shown for the other chromosomes in Figure 2. The clustering of epileptic cases in CNVs involving chromosome 4 points toward chromosome-specific susceptibility, warranting further investigation of gene content and dosage-sensitive regions on this chromosome.

Figure 2:

Graphical presentation of the number of patients with small chromosomal changes who have epilepsy, shown for each chromosome separately.

*(*No 23 = Chromosome Y, **No 24 = Chromosome X)*



The most common microdeletion syndromes in which epilepsy was diagnosed are Wolf-Hirschhorn syndrome (6/7 subjects), Angelman syndrome (3/5 subjects), and Williams syndrome (1/9 subjects). More detailed information regarding these syndromes and their electroclinical characteristics is given in Table 9.

Table 9:

Prevalence of epilepsy and the electroclinical phenotype in most common microdeletion syndromes with their genotype in our group of patients (group A+ group B1)

Syndrome	Microdeletion	No. of patients with epilepsy	Epilepsy type	Type of epilepsy	Type of epilep-tic seizure	Type of EEG finding	Age of first seizure	AET	Neuroimaging findings
Wolf-Hirschhorn syndrome	del4p	6/7	REF (4)	GEN (4)	PS (5)	HA (2)	< 1: 6	POLYTH (4)	NORM(5)
			CONT (2)	WS (2)	FwG (1)	F/MF (2)		MON-OTH (2)	ABN (1)
						G (2)			
Angelman syndrome	del15q 11-13	3/5	REF (3)	GEN (2)	GS (2)	G (2)	< 1: 2	POLYTH (3)	NORM (3)
				WS (1)	PS (1)	HA (1)	>1: 1		
Williams syndrome	del7q 11.23	1/9	REF (1)	WS (1)	PS IS (1)	HA (1)	< 1	POLYTH (1)	ABN (1)

The remaining small chromosomal changes in which epilepsy is more frequent are microCNVs on chromosome 4, chromosome 1, chromosome 10, chromosome 9, and chromosome 15. More details about the types of CNVs and their electroclinical characteristics are shown in Table 10.

Table 10:

Type of epilepsy, type of epileptic seizure and type of EEG findings found in number of patients with types (deletion/duplication) of small chromosomal changes shown for each chromosome number separately.

Chr	**Microdeletion/ microduplication**	**N**	**Epilepsy type (N)**	**Epilepsy type (N)**	**Epileptic seizure type (N)**	**EEG findings (N)**
1	Del1p	6	REF (3)	GEN (3)	FwG (3)	F/MF (2)
	Del1q21 (3)					G (2)
	dup1p13.3		CONT (3)	F (2)	GS (3)	HA (2)
	dup1q21.2			WS (1)		

2	Del2p	2	REF (2)	F (1)	FwG (1)	F/MF (1)
	del2q24.3			DS (1)	GS (1)	G (1)
3	del3p25.3	3	REF (1)	GEN (3)	FwG (1)	F/MF (2)
	del3q29		CONT (1)		GS (2)	HA (1)
	dup3p11.1					
4	Del4p (6)	8	REF (4)	GEN (6)	GS (2)	Norm (1)
	del4q13.1		CONT (4)	WS (2)	PS (5)	HA (2)
						F/MF (2)
	dup4q24				FwG (1)	G (3)
6	del6q22.1	1	CONT (1)	GEN (1)	GS (1)	MF (1)
7	Del7q11.23	3	REF (1)	GEN (2)	GS (2)	MF (1)
	dup7q31.1		CONT (2)	WS (1)	PS (1)	G (1)
	dup7q35					HA (1)
8	dup8p11.21p11.1x3	2	REF (2)	GEN (2)	GS (2)	G (1)
	dup8p23.3					
9	del9p24.3	4	REF (4)	GEN (2)	GS (1)	MF (2)
	dup9p del9p dup9q			F (2)	FwG (3)	G (1)
	del9q31.1 (2)					F (1)
10	del10q26.3	5	REF (3)	GEN (2)	FwG (2)	F/MF (2)
	dup10q25.3					
	del10q11.22			F (2)		G (2)
	dup10p13		CONT (2)		GS (3)	
	dup10q11.22			WS (1)		HA (1)
	dup10q22.2					
11	dup11p11.12	1	REF (1)	GEN (1)	GS (1)	G (1)
14	del14q11.2	1	REF (1)	GEN (1)	GS (1)	MF (1)
15	del15q11.2q13.1 (3)	5	REF (4)	GEN (3)	FwG (1)	F/MF (1)
	dup15q11.2q13.3		CONT (1)	F (1)	GS (3)	MF (1)
	del15q24.1			WS (1)	PS (1)	G (2)
						HA (1)

16	del16p11.2	3	REF (2)	GEN (1)	GS (2)	G (1)
	Del16p13.11		CONT (1)	WS (2)	PS (1)	HA (2)
	dup16q22.2					
17	dup17p11.2	1	REF (1)	GEN (1)	GS (1)	G (1)
18	del18p	2	REF (2)	GEN (1)	GS (2)	MF (1)
	dup18p11.32x4			WS (1)		HA (1)
19	del19p13.13	1	REF (1)	GEN (1)	GS (1)	G (1)
20	del20p11.1q11.1	2	REF (1)	GEN (1)	FwG (1)	F/MF (1)
	del20q		CONT (1)	F (1)	GS (1)	G (1)
21	del21q22.3	1	CONT (1)	GEN (1)	GS (1)	G (1)
22	dup22q11.21	1	CONT (1)	GEN (1)	GS (1)	G (1)
X	delXp22.12	3	REF (3)	GEN (2)	FwG (1)	F/MF (2)
	dupXp22.33x3			F (1)	PS (2)	G (1)
	dupXp11.23					
Y	dupYp11.2q11.22	2	REF (2)	F (1)	FwG (1)	F/MF (2)
	dupYq11.22.3			GEN (1)	GS (1)	

Abbreviations for Table 9 and Table 10					
Refractory	REF	Focal with generalization	FwG	Monotherapy	MONOTH
Controlled	CONT	Infantile spasms	IS	Normal finding	NORM
Generalized	GEN	Focal/ multifocal discharges	F/MF	With abnormalities	ABN
West syndrome	WS	Generalized discharges	G	Generalized seizure	GS
Polymorphic seizures	PS	Polytherapy	POLYTH	Hypsarrhyth-mia	HA
Focal epilepsy	F	Dravet sy	DS	Number of patients	N

Discussion

In this study, aCGH analysis identified CNVs in approximately three-quarters of the tested children, supporting its diagnostic utility in the evaluation of neurodevelopmental disorders and epilepsy. Although microdeletions were more frequently observed, the CNV subtype alone did not appear sufficient to account for the range of phenotypes seen. Moreover, epilepsy risk may be influenced by CNV size, gene content, and involvement of recurrent pathogenic loci, rather than by deletion versus duplication status alone (Miller et al., 2010; Cooper et al., 2011; Mefford et al., 2011; Coe et al., 2014; Olson et al., 2014).

Neurodevelopmental impairment was a prominent feature in CNV-positive patients. Motor deficit occurred more often in patients with microdeletions, consistent with the stronger impact of haploinsufficiency on dosage-sensitive genes involved in development (Miller et al., 2010; Cooper et al., 2011; Coe et al., 2014). Regardless of CNVs subtype, cognitive impairment was present in nearly all patients, reflecting a common outcome of diverse genomic rearrangements (Girirajan et al., 2012; Olson et al., 2014). Dysmorphic features were frequent but showed no meaningful association with epilepsy status, in keeping with evidence that dysmorphia reflects genomic imbalance rather than epileptogenic mechanisms.

Epilepsy affected more than half of the patients and was strongly associated with CNV presence, showing a markedly higher prevalence of refractory epilepsy. These results support earlier reports demonstrating a higher prevalence of rare CNVs in drug-resistant epilepsy and developmental and epileptic encephalopathies (Mefford et al., 2010; Berg et al., 2010; Mefford et al., 2011; Møller et al., 2015). Seizure phenotype appeared to vary with genetic status, with polymorphic seizures more often observed in refractory epilepsy and generalized seizures more commonly seen in controlled epilepsy. These observations may be consistent with underlying network involvement in genetic epilepsy, although alternative explanations are considered as possible (Mefford et al., 2011; Coppola et al., 2019).

Patients with CNVs more often experienced seizure onset within the first year of life and more frequently required polytherapy, features commonly associated with greater epilepsy severity and less favorable prognosis (Berg et al., 2010; Mefford et al., 2011). The predominance of normal neuroimaging findings suggests that genetic epilepsies are mainly characterized by molecular and circuit-level disturbances, rather than by gross structural abnormalities (Gaillard et al., 2009; Barkovich et al., 2015). EEG abnormalities were prevalent and varied across groups;

meanwhile, CNV-positive patients, especially those with refractory epilepsy, more often showed generalized discharges and severe EEG patterns such as hypsarrhythmia, suggesting widespread network disruption (Mefford et al., 2011; Olson et al., 2014; Scheffer et al., 2017).

Significant electroclinical heterogeneity was evident at the chromosome level, with clustering of epilepsy in CNVs affecting chromosomes 4, 15, 1, 9, and 10. The prominence of chromosome 4, especially the 4p and 4q regions, aligns with known genotype–phenotype correlations, including Wolf–Hirschhorn syndrome (Zollino et al., 2014; Paprocka et al., 2024). CNVs at 15q11–q13 and other recurrent loci showed similarly diverse epilepsy phenotypes, showing the importance of locus-specific interpretation (Helbig et al., 2009; Ben-Shachar et al., 2009; Mefford et al., 2011).

Our findings suggest that CNVs may be associated with epilepsy through disruption of neurodevelopmental networks, with potential effects on seizure type and severity, EEG features, and treatment response. Broad CNV classification alone may not be sufficient to consistently predict clinical outcomes, and more detailed locus and gene-level interpretation could be helpful in improving clinical interpretation.

The strengths of this study include the integration of genomic data with detailed electroclinical phenotyping and the direct comparison between CNV-positive and CNV-negative epilepsy, which permits clinically relevant, locus-oriented observations. However, the findings should be interpreted with caution, particularly in light of the relatively small sample sizes for individual CNV loci. Future multicenter studies with larger cohorts, systematic gene-level CNV interpretation, and longitudinal electroclinical follow-up will be important to further clarify genotype–phenotype relationships and support the development of precision medicine approaches in epilepsy.

Conclusion

Determining the electroclinical features of epilepsy in relation to the occurrence of small chromosomal changes may, in the future, provide a more appropriate classification of epilepsies and provide key information in identifying the role of genes involved in the development of epilepsy. Knowledge about the outcome of epilepsy may be enriched, and the application of targeted antiepileptic therapy based on specific chromosomal changes may be possible.

Declaration of Originality and Authorship

All authors state that the submission of this article is based on original work and neither has been published elsewhere in whole or in part, in any print or electronic media, nor is it under consideration by another journal for publication.

The manuscript has been read and approved by all authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Informed Consent

The authors declare that written informed consent was obtained from the patients for publication of this original research work. This study was approved by the institutional ethics committee of the Medical faculty, University St. Cyril and Methodius, in Skopje, North Macedonia (Ethics Committee for human research). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable national guidelines. Patient confidentiality was strictly maintained throughout the study.

Ethics committee for human research of the Medical faculty, University Street, Cyril and Methodius, in Skopje, North Macedonia, issued approval no. 03-525/8, for the conduct of the study.

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