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Identifying Prognostic Factors for Drug-Resistant Epilepsy in Children with Cerebral Palsy

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Abstract: Background and purpose: Drug-resistant epilepsy is a common and disabling complication in children with cerebral palsy (CP). This study aimed to analyze the relationship between neurological, functional, and perinatal factors and the development of drug-resistant epilepsy in pediatric patients with CP to determine prognostic factors and improve medical management. **Methods:** We compared three groups of patients with cerebral palsy: those with drug-resistant epilepsy, those with drug-sensitive epilepsy, and those without epilepsy. Clinical variables, perinatal history, characteristics of seizure onset, neuroimaging findings, functional scales (GMFCS, MACS), and comorbidities were collected. Associations were evaluated using appropriate statistical tests, including Fisher's exact test, multiple logistic regression, and inferential statistics in Epi Info™ version 7.2. **Results:** We studied 80 patients. Drug-resistant epilepsy was present in 49 (61%) of the participants. It was significantly associated with quadriplegic motor involvement (p=0.04), early seizure onset (p=0.03), and corticosubcortical atrophy on neuroimaging (20%, n=16). The need for gastrostomy (p=0.03) and the use of dual therapy (p=0.06) or polytherapy (p=0.008) were also strongly related to drug resistance. **Conclusions:** Drug-resistant epilepsy in children with CP is strongly linked to markers of severe neurological compromise and early epileptic manifestations, rather than to isolated perinatal complications. Early identification of high-risk profiles may guide timely diagnostic and therapeutic strategies to improve clinical outcomes.

Keywords: Cerebral Palsy, Drug-Resistant Epilepsy, Prognostic Factors, Child Development Disorder.

INTRODUCTION

Cerebral palsy (CP) comprises a group of permanent disorders of movement and posture resulting from disturbances in the developing central nervous system [1]. It represents the leading cause of motor disability in childhood, with a prevalence of 2–3 cases/1,000 live births [2-3].

CP arises from diverse etiological factors that may act during the prenatal, perinatal, or postnatal periods [4]. According to the predominant motor disturbance, CP is categorized into spastic (the most frequent subtype), dyskinetic, and ataxic forms. When classified by topography, motor involvement may be quadriplegic, hemiplegic, diplegic, or monoplegic [5].

The severity of motor impairment is commonly described using the Gross Motor Function Classification System (GMFCS) [6], a five-level scale that stratifies functional mobility across different age groups and reflects clinically meaningful differences in daily

motor performance. Complementarily, the Manual Ability Classification System (MACS) [7] provides a five-level framework to characterize hand function in children aged 4 to 18 years.

Magnetic resonance imaging (MRI) frequently shows structural abnormalities correlated with CP subtype [8]. In addition, genetic advances have identified monogenic forms, such as KANK1, AP4M1, and GAD1, encompassing autosomal recessive, autosomal dominant, and X-linked modes of inheritance [9].

Epilepsy is frequently regarded as a marker of greater clinical severity in CP due to its impact on motor outcomes, cognition, behavior, schooling, and overall quality of life [10]. Up to 40% develop drug-resistant epilepsy [11]. The International League Against Epilepsy (ILAE) has provided a definition for drug-resistant epilepsy (DRE) in 2010: “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”.

Regarding predictors of drug-resistant epilepsy in CP, evidence suggests that term-born infants are at higher risk, likely attributable to the predominance of gray matter injuries and cortical malformations, which are more epileptogenic than the white matter lesions typical of preterm infants. The prevalence of epilepsy also varies among CP subtypes: the highest rates are observed in bilateral spastic (tetraplegic) and dyskinetic CP.

While basal ganglia damage seen in dyskinetic CP does not inherently generate seizures, cortical lesions (secondary to hypoxic-ischemic injury) may increase epileptogenic potential by altering thalamocortical inhibitory circuits. Moreover, epilepsy shows a strong association with intellectual disability and with the severity of motor and non-motor impairments (levels IV-V of the GMFCS and MACS).

PURPOSE

To determine the prognostic factors of drug-resistant epilepsy vs drug-sensitive epilepsy in children with cerebral palsy (CP) and to review the therapeutic approach and clinical characteristics in both groups.

METHODS

This is an observational, analytical, retrospective case-control study to be conducted in children with CP and drug-resistant epilepsy in Pediatric Neurology Department of General Hospital Zone No. 33 of Mexican Social Security Institute in Monterrey, Nuevo León, Mexico. Data were collected from 80 children aged 2 months to 18 years.

This study was conducted in accordance with the ethical standards of Helsinki Declaration. The research protocol was reviewed and approved by the Comité Local de Investigación en Salud 1909, approval number R-2025-1909-009. Informed consent was obtained from relatives.

Three groups were compared: children with drug-resistant epilepsy (n=49), with drug-sensitive epilepsy (n=17), and without epilepsy (n=14). Data were collected on three groups: general characteristics (age, gender, gestational age, birth weight, intensive care unit stay, mechanical ventilation, causes of CP, hyperbilirubinemia and intraventricular

hemorrhage), characteristics of cerebral palsy (type, area of presentation, Gross Motor Function Classification System (GMFCS), Manual Ability Classification System (MACS) and mini MACS (for children under four years old), intellectual disability, visual, hearing and language impairment, microcephaly, tracheostomy, gastrostomy, ventriculoperitoneal shunt, physiotherapy and alternative therapies), characteristics of epilepsy (onset of epileptic seizures, type of epilepsy, abnormalities in the electroencephalogram, abnormalities in the magnetic resonance imaging, medication, genetic syndromes).

Intellectual disability is a lifelong condition characterized by significant limitations in intellectual functioning (IQ Intelligence quotient below 70 in The Wechsler Intelligence Scale WISC-V) and adaptive behaviors—such as conceptual, social, and practical skills—originating before age 18.

Language impairment was defined as a score below 70 on the Verbal Comprehension Index (VCI) of the WISC-V.

Visual and hearing impairment were defined by abnormal visual and auditory evoked potentials.

Microcephaly is a neurological condition defined as a head circumference that is significantly smaller than expected (typically 2 or more standard deviations below the mean) for a baby's age, sex, and population.

We used Fisher's exact test, logistic-multi regression, and inferential statistics in Epi Info™ version 7.2. Only includes data from patients who presented the characteristics.

RESULTS

A total of 80 patients were studied. Drug-resistant epilepsy was in 49 patients (61.25%), 17 patients (21.25%) had drug-sensitive epilepsy, and 14 patients (17.5%) never had epilepsy.

General Characteristics

Mean age was 8 years old (drug-resistant epilepsy: 9.04±5.2; drug-sensitive epilepsy: 8.2±3.8; without epilepsy: 6.2±4.8), range 2 months-17 years old, SD 4.93.

Fifty-seven percent were male, with male predominance in drug-resistant and drug-sensitive groups; the non-epileptic group showed equal distribution.

Mean gestational age was 35 weeks. Most patients (57%) were born >37 weeks, a pattern consistent across groups. Average birth weight was 2522 g; 57.5% weighed >2500 g, also predominating in all groups.

Intensive Care Unit (ICU) admission occurred in 72.5% of patients, with a mean stay of 26 days. Most children with epilepsy stayed 1 week to 1 month; the non-epileptic group showed no clear pattern. Mechanical ventilation was required in 42% overall, but was most common in the non-epileptic group. Ventilation duration averaged 5 days.

The predominant pre-perinatal cause of injury was neonatal hypoxia (50%), followed by congenital hydrocephalus and other less frequent etiologies. Postnatal causes included status epilepticus (13.75%), neuroinfection, traumatic brain injury, sepsis, and hypoxia. Neonatal hypoxia was the leading etiology in all groups.

Hyperbilirubinemia was uncommon: 13% received phototherapy, 5% exchange transfusion, and 81% had none. Most patients across groups had no hyperbilirubinemia.

Intraventricular hemorrhage was rare (10% overall), with grade 4 cases occurring in the drug-resistant group and grade 2 in a small subset; no cases appeared in the drug-sensitive group (Table 1).

Table 1: General characteristics of patients*

Characteristics	No epilepsy (n=14) (17%)	Drug-sensitive epilepsy (n=17) (21%)	Drug-resistant epilepsy (n=49) (61%)	Total (n=80) (100%)
Age (yr), SD	6.2±4.8	8.2±3.8	9.04±5.2	8.3±4.93
Gender				
Female	7 (50%)	8 (47%)	19 (38%)	34 (42%)
Male	7 (50%)	9 (52%)	30 (61%)	46 (57%)
Gestational age				
<32 weeks	4 (28%)	4 (23%)	11 (22%)	19 (23%)
33-36 weeks	4 (28%)	2 (11%)	9 (18%)	15 (18%)
>37 weeks	6 (42%)	11 (64%)	29 (59%)	46 (57%)
mean, SD	35±4.1	36±4.1	35±4.2	35±4.16
Birth weight				
<1500 g	3 (21%)	3 (17%)	8 (16%)	14 (17%)
1500-2500 g	5 (35%)	4 (23%)	11 (22%)	20 (25%)
>2500 g	6 (42%)	10 (58%)	30 (61%)	46 (57%)
mean, SD	2281±822	2490±757	2603±904	2522±859
Stay in ICU				
<7 days	3 (21%)	1 (5%)	7 (14%)	11 (13%)
8-31 days	4 (28%)	7 (41%)	16 (32%)	27 (33%)
>32 days	4 (28%)	3 (17%)	13 (26%)	20 (25%)
Mean, SD	21±27	22±29	29±52	26±44
Mechanical ventilation				
1-30 days	8 (57%)	8 (47%)	16 (32%)	32 (40%)
31-60 days	0	0	1 (2%)	1 (1%)
>61 days	0	1 (5%)	0	1 (1%)
Mean, SD	4±4	8±19	4±10	5±12
Causes of CP				
Pre-Perinatal				
-Neonatal Hypoxia	9 (64%)	7 (41%)	24 (48%)	40 (50%)
-Congenital hydrocephalus	0	3 (17%)	8 (16%)	11 (13%)
-Others	2 (14%)	1 (5%)	2 (4%)	5 (6%)
Post Natal				
-Status epilepticus	0	2 (11%)	9 (18%)	11 (13%)
-Others	3 (21%)	4 (23%)	6 (12%)	13 (16%)
Hyperbilirubinemia				
Phototherapy	3 (21%)	3 (17%)	5 (10%)	11 (13%)
Exchange transfusion	1 (7%)	0	3 (6%)	4 (5%)
Intraventricular hemorrhage				
Grade 1	1 (7%)	0	2 (4%)	3 (3%)
Grade 2	2 (14%)	0	0	2 (2%)
Grade 3	0	0	0	0
Grade 4	0	0	3 (6%)	3 (3%)

*Note: This table only includes data from patients who presented the characteristics, as detailed in the methods section.

Characteristics of Cerebral Palsy

Spastic CP predominated (96%), followed by dyskinetic (2%) and mixed (1%). Quadriplegia was the most common presentation (71%), with smaller proportions of hemiplegia, diplegia, paraplegia, and monoplegia. Spastic type and quadriplegia were dominant across all epilepsy groups.

Severe motor impairment was common: GMFCS level V in 89% and MACS level V in 87%, with similar predominance in all groups.

Severe intellectual disability was most frequent (50%), followed by global developmental delay (33%); severe disability predominated in drug-resistant and drug-sensitive epilepsy, while developmental delay was more common without epilepsy.

Visual impairment occurred in 25%, hearing impairment in 11%, and language impairment in 85%, the latter especially in epilepsy groups. Microcephaly was present in 15%. Tracheostomy occurred only in drug-resistant epilepsy (5%). Gastrostomy was present in 13%, mostly in drug-resistant epilepsy.

A ventriculoperitoneal shunt was found in 13 patients, nearly half dysfunctional; most cases occurred in drug-resistant epilepsy. Physiotherapy was used by 66%, more frequently in non-epileptic and drug-sensitive groups. Alternative therapies included omega-3 (3%) and botulinum toxin (16%). Dystonia occurred in 2 patients; no autism was reported (Table 2).

Table 2: Characteristics of cerebral palsy*.

Characteristics	No epilepsy (n=14) (17%)	Drug-sensitive epilepsy (n=17) (21%)	Drug-resistant epilepsy (n=49) (61%)	Total (n=80) (100%)
Type of CP				
Spasticity	14 (100%)	16 (94%)	47 (95%)	77 (96%)
Dyskinesia	0	1 (5%)	1 (2%)	2 (2%)
Ataxia	0	0	0	0
Mixed	0	0	1(2%)	1 (1%)
Presentation area				
Monoplegia	1 (7%)	1 (5%)	0	2 (2%)
Diplegia	4 (28%)	1 (5%)	3 (6%)	8 (10%)
Hemiplegia	2 (14%)	2 (11%)	5 (10)	9 (11%)
Quadriplegia	5 (35%)	12 (70%)	40 (81%)	57 (71%)
Paraplegia	2 (14%)	1 (5%)	1 (2%)	4 (5%)
GMFCS				
Level I	0	0	1 (2%)	1 (1%)
Level II	1 (7%)	1 (5%)	3 (6%)	5 (6%)
Level III	1 (7%)	1 (5%)	0	2 (2%)
Level IV	0	1 (5%)	0	1 (1%)
Level V	12 (85%)	14 (82%)	45 (81%)	71 (88%)
MACS				
Level I	1 (7%)	0	1 (2%)	2 (2.5%)
Level II	0	1 (5%)	1 (2%)	2 (2.5%)
Level III	1 (7%)	0	1 (2%)	2 (2.5%)
Level IV	1 (7%)	2 (11%)	1 (2%)	4 (5%)
Level V	11 (78%)	14 (82%)	45 (91%)	70 (87%)

Intellectual disability				
Mild	0	3 (17%)	4 (8%)	7 (8%)
Moderate	1 (7%)	1 (5%)	1 (2%)	3 (3%)
Severe	5 (35%)	7 (41%)	28 (57%)	40 (50%)
Profound	1 (7%)	0	2 (4%)	3 (3%)
Global developmental	7 (50%)	6 (35%)	14 (28%)	27 (33%)
Visual impairment				
Yes	5 (35%)	6 (35%)	9 (18%)	20 (25%)
Hearing impairment				
Yes	0	2 (11%)	7 (14%)	9 (11%)
Language impairment				
Yes	11 (78%)	14 (82%)	43 (87%)	68 (85%)
Microcephaly				
Yes	1 (7%)	4 (23%)	7 (14%)	12 (15%)
Tracheostomy				
Yes	0	0	4 (8%)	4 (5%)
Gastrostomy				
Yes	0	1 (5%)	9 (18%)	10 (13%)
Ventriculo peritoneal shunt				
Functional	0	1 (5%)	6 (12%)	7 (9%)
Dysfunctional	0	1 (5%)	5 (10%)	6 (8%)
Physiotherapy				
Yes	12 (85%)	14 (82%)	28 (57%)	54 (68%)
Alternative therapies				
Omega 3	0	1 (5%)	1 (2%)	2 (3%)
Botulinum toxin	6 (42%)	3 (17%)	4 (8%)	13 (16%)

*Note: This table only includes data from patients who presented the characteristics, as detailed in the methods section.

Characteristics of Epilepsy

Seizures began in the neonatal period in 21%, between 1 month–1 year in 43% (most common), and after 1 year in 17%, similar across epilepsy groups. Focal seizures were most frequent (31%), followed by generalized spasms (17%); focal seizures predominated in both drug-resistant and drug-sensitive epilepsy. The most frequently observed manifestation was versive (8%, n=7).

Electroencephalogram (EEG) abnormalities were present in 47%; 16% were normal, and 36% had no study. In drug-resistant epilepsy, normal and temporal focal abnormalities were equally common (12% each). In drug-sensitive epilepsy, temporal and occipital focal abnormalities were also equally frequent (11% each). Patients without epilepsy had mainly normal EEGs. Focal abnormalities occurred in 20%, multifocal in 26%, and hypsarrhythmia in one drug-resistant case.

MRI most often showed gray matter lesions (20%), particularly cortico-subcortical atrophy in epileptic groups; white matter injury predominated without epilepsy.

Levetiracetam was the most used drug (12%). Monotherapy was used in 31%, bitherapy in 27%, and polytherapy in 21%. Sixteen patients (20%) received no medication.

Nine patients had genetic syndromes, with Lennox-Gastaut being most common (4%), mainly in drug-resistant epilepsy. Other identified syndromes included mitochondrial

depletion, CUCLA2 mutation, and West syndrome. Two patients with temporal cortical dysplasia underwent amygdalohippocampectomy (Table 3).

Table 3: Characteristics of epilepsy*.

Characteristics	No epilepsy (n=14) (17%)	Drug-sensitive epilepsy (n=17) (21%)	Drug-resistant epilepsy (n=49) (61%)	Total (n=80) (100%)
Onset of epileptic seizures				
<1 month	0	3 (17%)	14 (28%)	17 (21%)
1 month – 1 year	0	10 (58%)	25 (51%)	35 (43%)
>1 year	0	4 (23%)	10 (20%)	14 (17%)
Type of epilepsy				
Focal (focal epileptic seizure with impaired awareness, with observable manifestations)	0	6 (35%)	19 (38%)	25 (31%)
Generalized type (generalized epileptic spasms)	0	4 (23%)	10 (20%)	14 (17%)
EEG				
Focal	0	5 (29%)	11 (22%)	16 (20%)
Multifocal	1 (7%)	5 (29%)	15 (30%)	21 (26%)
Hypsarrthymia	0	0	1 (2%)	1 (1%)
MRI				
Gray matter lesion (corticosubcortical atrophy)	0	5 (29%)	11 (22%)	16 (20%)
White matter lesion (hypoxic-ischemic insult)	4 (28%)	1 (5%)	4 (8%)	9 (11%)
Medication				
Monotherapy	0	9 (52%)	16 (32%)	25 (31%)
Bitherapy	0	4 (23%)+	18 (36%)	22 (27%)
Polypharmacy	0	2 (2%)+	15 (30%)	17 (21%)
Genetic syndromes	0	0	3 (6%)	3 (4%)
Lennox-Gastaut syndrome	0	1 (5%)	0	1 (1%)
Mitochondrial DNA depletion syndrome, CUCLA2 carrier	0	1 (5%)	0	1 (1%)
West syndrome	0	1 (5%)	0	1 (1%)

*Note: This table only includes data from patients who presented the characteristics, as detailed in the methods section.

+If the patient, despite having tried 3 drugs unsuccessfully in the past, now responds (is "seizure-free") to the current combination, the epilepsy is considered to be controlled.

We used Fisher's exact test to compare children with drug-resistant epilepsy (n=49), with drug-sensitive epilepsy (n=17), and without epilepsy (n=14) for each of the general characteristics, characteristics of cerebral palsy, and characteristics of epilepsy finding statistical significance for the variables quadriplegia (OR 3.6, *p* 0.01), gastrostomy (OR 6.7, *p* 0.04), bitherapy (OR 3.9, *p* 0.01), polypharmacy (OR 6.3, *p* 0.008),. and onset of epileptic seizures <1 month (OR 3.7, *p* 0.03) (Table 4). Logistic regression was subsequently used for these latter variables, finding that the most statistically significant and with the highest risk for drug-resistant epilepsy were gastrostomy (OR 10.61, *p* 0.03), onset of epileptic seizures <1 month (OR 4.68, *p* 0.03), and quadriplegia (OR 3.23, *p* 0.04) (Table 5).

Table 4: Fisher's exact test comparing subjects with and without drug-resistant epilepsy.

Independent variables		Presence of drug-resistant epilepsy		Fisher´s exact test *p* value equals	Odds Ratio	95% Confidence intervals
		Yes	No			
Quadriplegia	Yes	40	17	0.01	3.6	1.3±10.0
	No	9	14			
Gastrostomy	Yes	9	1	0.04	6.7	0.8±56
	No	40	30			
Bitherapy	Yes	18	4	0.01	3.9	1.18±13
	No	31	27			
Onset of epileptic seizures <1 month	Yes	14	3	0.03	3.7	0.9±14.2
	No	35	28			
Polypharmacy	Yes	15	2	0.008	6.3	1.3±30
	No	34	29			

Table 5: Logistic multi-regression. The dependent variable was drug-resistant epilepsy.

Variable	Odds Ratio	95%	C.I.	Coefficient	S.E.	Z-Statistic	P- Value
Quadriplegia	3.23	1.04	9.99	1.17	0.57	2.04	0.04
Gastrostomy	10.61	1.16	96.81	2.36	1.12	2.09	0.03
Bitherapy	3.36	0.93	12.06	1.21	0.65	1.86	0.06
Onset of epileptic seizures <1 month	4.68	1.13	19.24	1.54	0.72	2.14	0.03

DISCUSSION

In this study, drug-resistant epilepsy was highly prevalent among children with CP, accounting for more than half of the cohort (n=49) (61%) within a sample of 80 patients with CP.

This proportion aligns with previous reports indicating that epilepsy in CP frequently follows a complex clinical course[12] and that up to 30-40% of patients may develop drug-resistance [13]. Our findings reinforce the notion that epilepsy in this population reflects more severe underlying brain injury and greater neurological compromise.

Although gestational age and birth weight did not emerge as significant predictors of drug resistance, most children in all groups were born at term and weighed more than 2500 grams, consistent with literature suggesting that term infants-more likely to present gray matter injuries or cortical malformations-have a higher risk of developing epilepsy [14]. Neonatal hypoxia was the most frequent perinatal insult, reflecting patterns already described as strongly associated with both cerebral palsy and epileptogenesis [15].

In our cohort, the need for ICU admission did not show a significant association with drug-resistant epilepsy, even though most patients with drug-resistant epilepsy and without epilepsy groups required hospitalization ranging from 8 days to 31 days (mean 26 days±44). This finding suggests that ICU stay reflects the severity of the perinatal insult rather than serving as a predictor of later drug-resistant epilepsy [16].

Similarly, mechanical ventilation was not associated with drug resistance; in fact, a higher proportion of patients without epilepsy required ventilatory support, which supports the notion that mechanical ventilation depends more on acute respiratory compromise than on subsequent neurologic risk [17].

Regarding hyperbilirubinemia, most neonates in our study did not present this condition, and among those who did, the majority required only phototherapy while few underwent exchange transfusion. Accordingly, hyperbilirubinemia did not emerge as a factor related to epilepsy or drug-resistance, consistent with reports indicating that elevated bilirubin alone rarely leads to long-term neurological sequelae when not accompanied by other perinatal stressors [18].

Regarding intraventricular hemorrhage, its overall incidence in our cohort was low. Although isolated cases of grade IV intraventricular hemorrhage were identified in children with drug-resistant epilepsy, the sample of grade IV intraventricular hemorrhage was small (n=3) to establish a definitive association. Nevertheless, this observation aligns with previous studies showing that only severe intraventricular hemorrhage (grades III and IV) confers a higher risk of subsequent epilepsy and long-term neurodevelopmental impairment [19-20].

Regarding CP characteristics, quadriplegia was significantly associated with drug-resistant epilepsy in bivariate analysis [21]. This is consistent with prior studies demonstrating that more extensive motor impairment (quadriplegia) correlates with a higher risk of severe epilepsy and poorer seizure control. Similarly, the predominance of GMFCS and MACS level V among children with drug-resistance highlights the relationship between severe functional impairment, global neurological dysfunction, and increased epileptogenic potential [22].

The presence of severe intellectual disability (n=30, 61%) is consistent with what has been reported in previous studies. A recent systematic review found that severe intellectual disability is among the heterogeneous contributors to the high prevalence of epilepsy in CP [23]. Furthermore, in another study with children with moderate to severe CP, only 22.5% had normal intelligence, while the rest had moderate or severe intellectual disability (41.3%); the presence of epilepsy was associated with a lower intelligence quotient (IQ) in this group [24].

Visual disturbances are a common comorbidity in CP: a recent multicenter study reports that 93.2% of children with cerebral palsy had some degree of visual impairment assessed clinically and/or through visual evoked potentials [25]; however, in our study, visual impairment was only present in 20 patients (25%).

In a retrospective study on pediatric populations with CP, it was observed that children with hearing impairment have a significantly higher risk of developing epilepsy; however, this characteristic has not been independently associated with drug resistance [26]. In our cohort, this comorbidity also did not show a significant association with drug resistance.

In our study, the majority of patients (n=68) had language impairments, with higher prevalence in drug-resistant patients (n=43). The clear predominance of language disorders in the drug-resistant group supports the interpretation that language involvement acts as a clinical marker of greater cortical or corticosubcortical compromise, a pattern that aligns

with studies showing that lesions located in eloquent functional networks increase the likelihood of drug-resistant epilepsy [27].

In our study, the low absolute frequency of microcephaly (n=12) prevents us from stating that it is an independent predictor of drug resistance. Recent literature shows heterogeneous results. A retrospective study found a high prevalence of microcephaly in children with CP and epilepsy, but it did not observe significant differences between those with and without epilepsy, suggesting that microcephaly can coexist with epilepsy without being a strong predictor of it on its own [28].

Recent series report that up to 18% of children with CP who require airway support via tracheostomy had, at the time of the procedure, indications such as ventilatory dependence or recurrent aspiration, but no association was found with the presence of epilepsy [29]; this implies that the direct relationship between drug-resistant epilepsy and the need for tracheostomy is not well documented, similar to our study that was only found in 5% (n= 4).

Gastrostomy also showed an association with drug-resistant epilepsy, likely reflecting greater overall clinical severity rather than a direct causal relationship. Children who require gastrostomy often have profound motor disability, dysphagia, and a high overall clinical severity, which could be associated with an increased risk of drug-resistant epilepsy in children with CP [30].

Although the use of a ventriculoperitoneal shunt is well established for the management of hydrocephalus, its role in the context of drug-resistant epilepsy in children with CP is complex and controversial [31].

In our study, physiotherapy was less common in children with drug-resistant epilepsy (57%) than in the groups with controlled epilepsy (82%) and without epilepsy (85%). This is consistent with what has been reported in an article indicating that patients with greater motor severity, comorbidities, and frequent seizures usually have more difficulty participating in intensive rehabilitation interventions. Although physiotherapy does not directly alter drug resistance, these patients tend to receive less rehabilitation due to functional and organizational limitations [32], which is consistent with the results observed in our cohort.

A recent systematic review and meta-analysis found moderate reductions in seizure frequency after omega-3 supplementation in pediatric studies of drug-resistant epilepsy, but the magnitude of the effect varies between trials, and the methodological quality is variable [33].

In our population, 13 patients (16%) received botulinum toxin injections for spasticity management. The use of botulinum toxin was clearly related to rehabilitation indications rather than attempts to control seizures [34].

Early seizure onset-particularly before one month of age-was associated with a markedly increased odds of drug-resistant. This finding is well supported by previous literature [35], where neonatal epileptic events often indicate severe structural or metabolic injury and predict a more intractable course. In our study, focal seizures, especially those with impaired awareness, predominated in the drug-resistant group. This pattern correlates with the predominance of cortical–subcortical lesions observed on MRI, which are well-known substrates for focal epileptogenesis [36-37].

Electroencephalographic abnormalities were more frequent in children with drug-resistant epilepsy, particularly multifocal discharges [38], reflecting diffuse or bilateral cortical injury. Only one child showed hypsarrhythmia, but the presence of Lennox-Gastaut syndrome in the drug-resistant group further emphasizes the severity of epilepsy in these patients.

The use of bitherapy and polypharmacy showed strong associations with drug-resistant epilepsy and remained significant in multivariate analysis. This relationship is expected, as patients with poor seizure control often require escalation to combined or multiple antiseizure medications. However, their significance in the regression model supports the clinical utility of these treatment patterns as markers of refractory disease rather than independent causal factors.

MRI findings in our cohort were consistent with previously documented associations: gray matter lesions (particularly cortical–subcortical atrophy) were most frequent in the drug-resistant and drug-sensitive groups, whereas white matter injury predominated among children without epilepsy. This distribution aligns with the widely accepted premise that gray matter involvement-especially due to hypoxic-ischemic injury-poses a higher epileptogenic risk [39-40].

Overall, the findings highlight a constellation of factors that characterize children with drug-resistant epilepsy in the context of CP:

(1) greater motor severity (quadriplegia, GMFCS/MACS V),

(2) early seizure onset (especially neonatal),

(3) cortical or corticosubcortical injury on MRI,

(4) need for gastrostomy as a marker of global neurological compromise, and

(5) requirement of bitherapy or polypharmacy.

These results are consistent with international evidence and contribute to a better understanding of prognostic factors in this population, allowing for earlier identification of children at high risk of drug resistance and more targeted therapeutic strategies.

CONCLUSION

In conclusion, the present study identified several independent predictors of drug-resistant -namely, quadriplegic motor involvement, severe functional limitation (GMFCS/MACS level V), early seizure onset (particularly during the neonatal period), cortical or cortico-subcortical lesions on neuroimaging, and the need for gastrostomy- underscoring that the severity and distribution of underlying brain injury play a more pivotal role than perinatal complications alone.

The association between gastrostomy requirement and drug-resistant epilepsy likely reflects the broader neurodevelopmental compromise, including severe motor impairment, dysphagia, and multisystem comorbidities, rather than a direct causal link. Likewise, the use of bitherapy or polytherapy in these patients highlights the complex therapeutic challenge posed by their refractory epileptic conditions and supports the notion that monotherapy may be insufficient in this subset.

Conversely, perinatal variables such as neonatal intensive-care unit stay, mechanical ventilation, hyperbilirubinemia, or intraventricular hemorrhage did not show a significant relationship with drug resistance, which suggests that while these factors mark early neonatal instability, they are not robust predictors of long-term refractory epilepsy. Instead, the presence of extensive structural brain abnormalities - particularly affecting cortical networks - appears to more directly influence the epileptogenic potential and long-term seizure outcomes.

Overall, our findings provide a more refined understanding of prognostic factors associated with drug-resistant epilepsy in CP. Early identification of high-risk patients - based on clinical, functional, and neuroimaging markers - may enable timely referral for advanced diagnostic evaluation, optimization of antiseizure treatment strategies, and consideration of non-pharmacological interventions when appropriate. Ultimately, this may improve neurological stability, functional outcomes, and quality of life for affected children and their families.

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