Patterns and Prognosis of Epileptic seizures in Children with Cerebral Palsy

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ABSTRACT:

BACKGROUND:

Cerebral palsy (CP) is the result of non-progressive damage to the developing brain and consists of a number of clinical neurological syndromes of heterogeneous etiology. Epilepsy is known to have a higher association with cerebral palsy; 15–60% of children with cerebral palsy have been reported to have epilepsy.

OBJECTIVE:

This study was performed to determine and assess the characteristics of cerebral palsy and explore the relationship between type of cerebral palsy and patterns of epileptic seizures and to determine the associated factors, nature and prognosis of epilepsy in children with cerebral palsy.

PATIENTS AND METHODS:

Design:A prospective, hospital-based, case-control study.

Setting: RaparinPediatric Teaching Hospital, Rizgary Teaching Hospital-Neurology Department and Helina Handicap Care Centre during the period of January 2013- July 2015, Erbil, KRG, Iraq.

PATIENTS:

One hundred and twelve children had CP and seizures were studied (group1). Two control groups included 70 children had CP without seizures (group2), and 50 children had seizures without CP (group3).

The following data were ascertained: Type of CP, pattern of seizures, age, gender, age at onset of seizures, mode of delivery, history of hypoxic ischemic encephalopathy in the neonatal period, neonatal seizures, history of status epilepticus, family history of seizures, developmental delay, EEG data, image findings, use of anti-epileptic drugs, seizures control and seizures outcome. Children with febrile convulsion were excluded from this study.

RESULTS:

Spastic tetraplegia wasthe most common type of CP (29.46%, 35.71%) in group 1 and 2 respectively.Generalized tonic, clonic or tonic clonic seizures were the most common types of seizures in both groups. Unlike those who had epilepsy without CP,themajority; 57(50.89%) of patients who had epilepsy and CPdeveloped seizures in the first year of life. Twenty eight percent of caseswith epilepsy and cerebral palsy, and 88% of cases with epilepsies alone showed good seizure control by antiepileptic therapy. Children who had epilepsy and CPhad a higher frequency of; neonatal seizures44 (39.28%), developmental delay98 (87.5), abnormal brain CT scan 91(81.25%) and family history of seizures47 (41.69%). Large number of patients who had epilepsy and CP 81(72.32%) needed poly therapy while majority ofthose who had epilepsy without CP needed single therapy 60(90%).

CONCLUSION:

Cerebral palsy is associated with a higher incidence of seizure disorders, whichin a majority has its onset in the first year life.Brain imaging showed abnormal pathology in most affected children and needed poly therapy and even difficult to control.

KEY WORDS: seizure, cerebral palsy; epilepsy, children.

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INTRODUCTION:

Cerebral palsy (CP) is the result of non-progressive damage to the developing brain and consists of a number of clinical neurological syndromes of heterogeneous etiology[(1)]. Cerebral palsy is known to have a higher association

withepilepsy; 15–60% of children with cerebral palsy have been reported to have epilepsy,[2] being maximum in patients with the quadriplegic type and minimum in those having the diplegic and athetoid types [3]. Mental retardation and epilepsy are more common in children with cerebral palsy[4]

CP can manifest itself in several ways, mainly as spastic, athetoid and ataxic palsies; moreover, it is one of the most common causes of motor disability in children and is frequently associated with other problems, such as mental retardation, sensory defects and epilepsy[5].

AIM OF THE STUDY:

This study was performed to determine and assess the characteristics of cerebral palsy and explore the relationship between type of cerebral palsy and patterns of epileptic seizures and to determine the associated factors, nature and prognosis of epilepsy in children with cerebral palsy.

PATIENT AND METHODS:

In a hospital-based,prospective, case-control study; 112 children with CP and seizures at Raparin Pediatric Teaching Hospital, Rizgary Teaching Hospital-Neurology Department and Helina Handicap Care Centre during the period of January 2013- July 2015 were studied (group1). Two control groups of 70 children had CP without seizures (group2) and 50 children had seizures without CP seen during this period (group3), were also studied**.**

Cerebral palsy was defined as motor disabilities caused by non-progressive damage to the developing brain[6].

Epilepsy was defined as separate occurrence of two or more apparently unprovoked seizures[7].Seizure outcome was defined as "good" if the patient remained seizure free for more than 1 year, "slightly controlled" if seizures occurred once a month or less, and "poor" if the patient suffered from daily or weekly seizures[8].

Epilepsies were classified in accordance with the International Classification of Epilepsies and Seizure disorders[9]. Patients were divided into CP types based upon the classification proposed by Michael V.Johnson et al. Spastic tetraplegia (spasticity of all four limbs with involvement of the arms more marked than or equal to that of the legs), spastic diplegia (spasticity of the lower extremities with a variable but a lesser degree of involvement of the upper limbs), spastic hemiplegia (spasticity of the arm and leg on one side), hypotonic and mixed forms (the last one is combination of previous types, as well as athetoid, ataxic and dystonic, due to small number of cases).

All the children were examined by a pediatrician and when required by a neurologist and their EEGs were studied by neurophysiologists or neurologists trained in neurophysiology and brain imaging studies were studied by a radiologists. The following data were ascertained: type of CP, type of epileptic seizure, age, gender, age at onset of seizures, mode of delivery, history of hypoxic ischemic encephalopathy in the neonatal period, neonatal seizures, history of status epilepticus, family history of seizures, developmental delay, EEG data, image findings, use of anti epileptic drugs, seizure control and seizure outcome and degree of disability (very severe: when patients do not have any postural control; severe: can walk with maximum support or, in hemiplegic patients do not have voluntary manual grasp; moderate: can walk with some support or when the patient globally used the paretic hand without possibility of individual movements of the fingers and; mild: can walk independently[11]. Children with febrile convulsion were excluded from this study.

RESULTS:

As the gender was matched; in group1, 2 and 3 there were equal number of boys and girls (56 each) , (35 each)and (25 each) respectively. The mean age of children ingroup 1 was 1.7 years (range 6 months –12 years), ingroup 2 was 4.9 years (range 2–14 years) and in group 3 was 5.3 years (range 6 months –14 years). In both groups of CP; spastic tetraplegia wasthe most common type of CP (29.46% of children in group 1 and 35.71% of children in group 2) as shown in Table-1.

About 42% of children with CP (group 1) presented with generalized (tonic, clonic or tonic clonic) seizures; however, 46% of epileptic children without CP (group 3) had generalized (tonic, clonic or tonic clonic) seizures and the difference was not significant in both groups.On the other hand, infantile spasm (10.7%) and polymorphic (9.8%) seizures were more common in group 1 than group 2 (2%, 6%) respectively.The difference was also not significant.Lenox gastaut syndrome was noted only in group 1,as shown in (Table- 2).

Table 1: Frequency of epilepsy in different types of cerebral palsy.

CP type		CP with seizure no.(%)	CP without seizure no.(%)
Spastic	Tetraplegia	33(29.46)	25(35.71)
	Diplagic	26(23.21)	11(15.71)
	Hemiplagic	13(11.6)	9(12.85)
Hypotonic		14(20.5)	14(20)
Athetoid		12(10.71)	8(11.42)
Ataxic		3(2.67)	3(4.28)
Mixed		11(9.82)	14(20)
Total		112(100)	70(100)

Table 2: Type of epilepsy in different forms of cerebral palsy and control group.

Types of epileptic seizures	Epileptic seizures with CP no.(%)	Epileptic seizures without CP no.(%)	p value
Generalized tonic, clonic or tonic clonic	47(41.96)	23(46)	0.7
Simple partial, complex	32(28.57)	18(32)	0.3
Myoclonic	7(6.25)	5(10)	0.39
Infantile spasm	12(10.7)	1(2)	0.05
Lenox gastaut syndrome	3(2.67)	0(0)	0.5
Polymorphic	11(9.8)	3(6)	0.5
Total	112(100)	50(100)	

The majority of patients in group one developed epilepsy in the first year of life and very small number of patients developed epilepsy after 6 yeas of life, in contrast; majority of group 3 patients developed epilepsy after first year of life. A highly significant association was noted between early onset of epileptic seizures occurrence and presence of CP, as shown in (Table-3).

Table 3: Distribution of patients according to age at seizure onset.

Age at seizure onset	Tetraplagic CP	Diplagic CP	Hemiplagic CP	Hypotonic CP	Athetoid CP	ataxic CP	Mixed	Totalepilepssy with CP	Totalepilepssy without CP
< 1 year	16	14	5	9	6	1	6	57 (50.89)	7 (14)
1 - 6 years	12	11	8	5	5	2	5	48 (42.85)	29 (58)
> 6 years	5	1	0	0	1	0	0	7 (6.25)	14 (28)

P value: 0.001

There is a highly significant association between each ofhistory of neonatal seizures, history of status epileptics, family history of epilepsy and abnormal findings in the brain CTS and the occurrence of epilepsy (p values; 0.001, 0.001 and 0.01 respectively). Though statistically not significant,developmental delay and mental retardation were also more frequently reported in group1 than group 2.As shown in (table- 4).

Table 4: The association between some variables with development of epilepsy in cerebral palsy.

Variables	Cerebral pasly with seizure No. (%)	Cerebral palsy without seizure No. (%)	RR	p value
Neonata seizures	44(39.28)	5(7.14)	73.1	0.001
Developmental delay	98(87.5)	57(81.42)	1.5	0.2
Family history of epilepsy	47(41.96)	17(24.28)	1.1	0.01
Mental retardation	97(86.60)	47(67.14)	8	0.1
Status epilepticus	47(41.96)	12(17.14)	102	0.001
Abnormalities in brain CTS	91(81.25)	43(61.42)	2.7	0.01
Total	112(100)	70(100)		

Concerning the different types of epileptic seizures in cerebral palsy; generalized (tonic clonic, tonic or clonic) was more frequent in all types of cerebral palsy and it was more in spastic type, followed by hypotonic and athetoid.Partial epilepsy was the next common type in all groups of cerebral palsy and it was also more common in spastic cerebral paly, followed by hypotonic and lastly athetoid type. Infantile spasm also was more common in spastic cerebral palsy bat was largely equal to polymorphic type in all forms of cerebral palsy, all data are showed in figure 1.

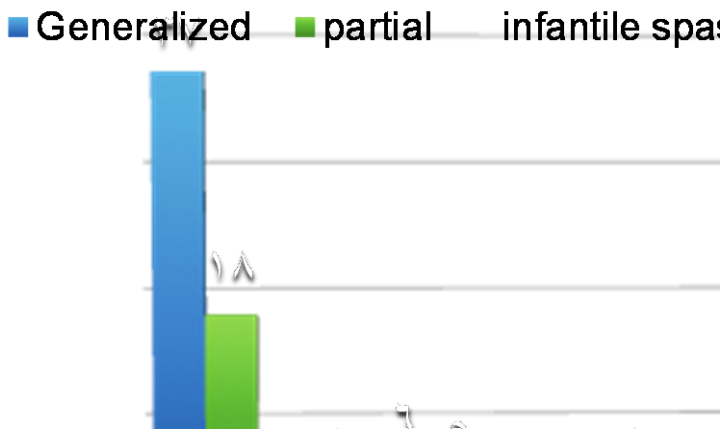

Figure 1: Frequency of epileptic seizurespatterns in different types of cerebral palsy.

Regarding the response to antiepileptic therapy; 28% of children with epilepsy and cerebral palsy, and 88% of those who had epilepsy without cerebral palsy showed good control , while 71.5% of children with epilepsy and cerebral palsyshowed bad response and only 12% of those who had epilepsy without cerebral palsy showed bad response (table -5).

Table 5:Seizures control in different types of cerebral palsy.

Seizure control	Tetraplegia no(%)	Diplagia no(%)	Hemiplagiano (%)	Hypotonic no (%)	Athetoidno(%)	Ataxicno (%)	Mixedno (%)	Totalno (%)	Group 3 no(%)	P value
Good control	16 (14.28)	7 (6.25)	6 (5.35)	4 (3.57)	3 (2.67)	2 (1.78)	2 (1.78)	32 (28.57)	44 (88)	0.001
Slight control	22 (19.64)	17 (15.17)	9 (8)	3 (2.67)	5 (4.46)	3 (2.67)	5 (4.46)	53 (47.32)	4 (8)	0.001
bad control	4 (3.57)	7 (6.25)	5 (4.46)	0 (0)	3 (2.67)	0 (0)	2 (1.78)	27 (24.10)	2 (4)	0.01

About32 %of casesin group 1and 2.85% of group 2 had history of neonatal seizures.The majority of epileptic patients with cerebral palsy used more than one therapy for control while vast majority of cases of epilepsy without cerebral palsy were controlled with one anticonvulsant. Brain CTS showed brain pathologies in 9(12.85%) of cases of epilepsy without cerebral palsy while 81.41% of cerebral palsies showed positive findings. EEG was conclusive in 69.64% in cases of cerebral palsy with epilepsy while it was just showed findings about 54% in epilepsy cases with no cerebral palsy as showed in (table-6).

Table 6:Factors that may be effective in seizure control in children with CP.

Factors	Epileptic seizures with CP no.(%)	Epileptic seizures without CP no.(%)	P value
Neonatal seizure	44(32.28)	2(3)	0.001
Poly therapy	81(72.32)	7(10)	0.001
CT findings	91(81.25)	9(12.85)	0.001
EEG findings	78(69.64)	27(54)	0.1

DISCUSSION:

The frequency of epilepsy varied with different forms of CP, a fact which was noted by many authors[2,12,13].It was highest (64.42%) in spastic cerebral palsy and lowest (2.67%) inataxic type, which might be a reflection of the severity of damage to the brain[12]. Tetraplegic CP was the most frequent among spastic CP and this agrees with Kwong et al who reported "tetraplegic CP had the highest prevalence"[2].Spastic diplegia was more common than hemiplegic type and this difference was more in CP with epilepsy group than CP without epilepsy group, possibly due to different types of underlying cause and brain damages as periventricular leucomalacia was mostly associated with spastic diplegia; a finding also reported by Gurseset al[14].

Both generalized and partial epilepsies were seen more in tetraplegia, then in diplegia followed by hemiplegia In the Hadjipanayis et al study, focal seizures were more common in spastic hemiplegics, whereas generalized seizures were more common in the other types [1]. In Aksuet al and Delgadolet astudies, focal seizures or secondary generalized seizures were more common in patients with CP[15, 16]. In Kwonget al and Gururajl et alstudies [2,13]; generalized epilepsies had the least prevalence, while polymorph seizures were the most common, also they added that classification of epileptic disorders in patients with CP was difficult because focal seizures soon become generalized.

Mental retardation was more frequent in children with CP and epilepsy than CP patients without epilepsy (86.6% vs. 67.14%). Kwong et al and Gururaj et al reported similar findings.[2,13]

Epilepsy in children with CP was associated with an earlier onset of seizures than in children without CP; 57 (50.89%) children with CP had epilepsy in their first year of life, compared to 7 (14%) children having seizures without CP. Zaferiou et al found that 69% of patients with CP had their first epileptic attack before they were a year old.[12]This indicates the severity of underlying brain injury.

This study showed that 38.5%(70 out of 182) of enrolled children with CP developed epilepsy.This agrees with

Kwong and Aksu studies where 47% and 38.5% children with CP developed epilepsy respectively [2, 15]. Sixteen cases (52%), whose brain CT scans showed structural disorders, had seizures within their first year of age. The association of neuroradiologic findings between early age and seizure onset has been described by Aksu[15].This can explainedby the fact that significant brain volume reduction, periventricular leucomalacia (PVL), basal ganglia changes, multicystic encephalopathy and schizencephaly were the major abnormalities seen.

Neonatal seizures were found to be more frequent in epilepsy with CP 44(32.28%) than in epilepsy without CP group 2(2.85%).The presence of neonatal seizure was considered to be a risk factor for subsequent development of neurologic disabilities, such as mental retardation, CP, or epilepsy [9,17,18]. Kwong et al noted neonatal seizures in 19% of children with CP and epilepsy, similar to the percentage noted in the patients with CP per se[2].

Levene reported that neonatal seizures had an adverse effect on neurodevelopmental progression and may predispose to cognitive, behavioral, or epileptic complications later in life.[19]

Mellitis et al showed that the incidence of mental retardation, CP or epilepsy following neonatal seizures rangedbetween 64% to 83%.[20]

Abnormal EEG findings were noted in about 70% ofepeleptics with CP and 54% of epiuleptics without CP .The difference was statistically not significant.EEG was documented as being the most useful method for the prognosis of neonatal seizures[13,18,19]. Status epilepticus is more common in patients with CP [13,17,18].In thisstudy; 47(41.96) cases of group one developed status epilepticus, while12 (17.14%) cases of status epilepticuswere found in the control group.In Kwonget al study; 88% of status epilepsies were reported in children with a neurological disorder.[2]

Controlling seizures in children with CP is more difficult than in those with normal brain development, and which is the reason for polytherapy. In this study, polytherapy was used 81(72.32%) of patients with CP, while just 7 (10%) of the controls needed polytherapy. Percentages of polytherapy usage in the Kwong[2]was 30 % and with Aksu[15] was 82%.

Good outcomes with therapy was reported in 32(28.57%) of children with epilepsy and CP, as compared to 44(88%) of those who had epilepsy without CP. Patients with ataxic and hypotonic CP had the best outcome while diplagic type had the worst control. Similar to these findings;Kwong et al reported, 37% of the study group, as compared to 90% of the controls had good outcomes.

In thisstudy,of the cases, 34% had bad outcomes, in comparison to 3% of controls group. Quadriplegics had the best outcome whilediplegic spastics had the worst outcomes. These findings were in agreement with the Gurarajet al and Delgadoet al sudies[13,16]. This may be due to the more extensive brain pathology seen on brain imaging in this group of children.

In the present study, as in A.K. Gururaj[14] study epilepsy was found to have an earlier age of onset, poorer seizure control, increased risks of status epilepticus and a need for more than one antiepileptic drug for seizure control in children with CP and seizures, There was also a higher prevalence of neonatal seizures in this group of children as compared with the other two control groups the prevalence being related to the severity and its associated disabilities. The outcome depends on the types of cerebral palsy. New antiepileptic drugs and advances in surgical interventions maybe promising.

In group 1, 57(50.89%) of children developed their first seizure in the first year of life and only 7(6.25%) had their first seizure after their 6th birthday. In the previous studies, Aksu and S.PourAhmadi found that the seizures started within 2 years in 50% of the children[14,16]. In children with epilepsy without CP, only 4% had seizures with an onset in the first year. The earlier onset of seizures, coupled with the need for more prolonged antiepileptic drug therapy and the use of polytherapy will pose a significant burden on these children with CP and seizures[19].

In comparison of children with CP with seizures and those without seizures, the following variables had an increased association with seizures: a history of neonatal seizures, mental retardation, history of status epileptics and abnormal brain CTS findings this is in agreement with Gururaj et al[14] studywho found that history of neonatal seizures, spastic tetraplegic variety of CP and presence of schizencephaly on brain imaging factors associated with increased association with seizure group.

CONCLUSION:

Cerebral palsy is associated with a higher incidence of seizure disorders, which in a majority has its onset in the first year life. Brain imaging showed abnormal pathology in most affected children and needed poly therapy and even difficult to control.

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