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Epilepsy in children with cerebral palsy

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Objectives: To study the occurrence, associated factors, nature and prognosis of seizures in children with cerebral palsy (CP).
Design: A prospective, descriptive, hospital-based, case-control study.
Setting: Tertiary level University Teaching Hospitals in the Al Ain Medical District, United Arab Emirates.
Patients: Fifty-six children with CP and seizures seen in the neurodevelopmental clinics at Al Ain and Tawam University Hospitals during the period of 1997–1999 were studied (group 1). Two control groups of 35 children with CP without seizures (group 2) and 50 children with seizures but no CP (group 3) were also studied.
Results: Spastic tetraplegia was the commonest type of CP associated with seizures whereas spastic diplegia was the commonest variety of CP in group 2. Most children with CP had an early onset of seizures within the first year of life as against those without CP. The children in group 1 had a higher incidence of neonatal seizures (42.9% vs. 29.4% in group 2 and 0% in group 3), presence of significant developmental delay (98.2% vs. 20.0% in group 3), occurrence of significant abnormalities on brain imaging (94.6% vs. 19.6% in group 3) and a need for use of more than 1 antiepileptic drug (66.1% vs. 30.0% in group 3). Over half of children in the study group presented with generalized tonic clonic seizures; the electroencephalogram (EEG) showed focal epileptic discharges with or without secondary generalization in 39.3%. The overall outcome of seizures in children with CP was poor needing prolonged course of anticonvulsant medications, polytherapy and higher incidence of refractory seizures and admissions for status epilepticus compared to the control group.
Conclusions: Cerebral palsy is associated with a higher incidence of seizure disorders, which, in a majority, has its onset in the neonatal period; brain imaging showed abnormal pathology in most affected children, which possibly accounts for the tendency to more refractory seizures in these children.

Key words: cerebral palsy; epilepsy; electroencephalography; hypoxic ischemic encephalopathy.

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 aetiology[1]. Epilepsy is known to have a higher association with cerebral palsy; 15–60% of children with cerebral palsy have been reported to have epilepsy[2]. It has been observed that seizures in these children tend to have an earlier onset, necessitating the use of more than 1 antiepileptic drug (AED) with the risk of seizure relapse after AED discontinuation[3, 4].

The objective of the study was to explore the relationship between cerebral palsy and epilepsy and to determine the occurrence, associated factors, nature and prognosis of epilepsy in children with cerebral palsy. We feel that this study differs from most other previous studies on CP and seizures since the comparison groups included children with CP but no seizures and children with seizures only.

PATIENTS AND METHODS

In a prospective, descriptive, hospital-based, case-control study, 56 children with CP and seizures seen at the Paediatric Neurodevelopmental clinics at Tawam and Al Ain University Teaching Hospitals during the periods of 1997–1999 were studied (group 1). Two control groups of 35 children with CP without seizures (group 2) and 50 children with

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seizures but no CP seen during this period (group 3) were also studied. CP was defined as motor and postural disabilities caused by non-progressive damage to the developing brain. Epilepsy was defined as occurrence of two or more unprovoked seizures in the absence of a primary metabolic or infective pathology in the brain. Epilepsies were classified in accordance with the International Classification of Epilepsies and Seizure disorders[5]. All the children were examined by a developmental paediatrician (G.A.) and their EEG and brain imaging studies were studied by a Paediatric neurologist (L.S.). The following data were ascertained: type of CP, type of epilepsy, age, sex, nationality, age of onset of seizures, details 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, brain CT/MRI findings, use of antiepileptic drugs, seizure control and seizure outcome. Good seizure control was defined by seizure-free period of over 12 months and poor seizure control was defined as daily or weekly recurrences.

Data processing, statistical methods and analysis

The data were coded and entered in to a computer and processed on an IBM compatible computer using Statistical Packages for Social Sciences [SPSS], Norusis. Data are expressed as mean and standard deviation (SD) unless otherwise stated. Student *t*-test was used to ascertain the significance of differences between mean values of two continuous variables and Mann–Whitney test was used for non-parametric distribution. Chi-square analysis was performed to test for differences in proportions of categorical variables between two or more groups. In 2×2 tables, the Fisher exact test (two-tailed) was used instead of Chi-square, when the sample size was small. The level $P < 0.05$ was considered as the cut-off value for significance.

RESULTS

In the study group, there were equal number of boys and girls (28 each); in group 2 (with cerebral palsy but no seizures) there were 16 boys and 19 girls and in group 3 (seizures only) there were 29 boys and 21 girls. The mean age of children in group 1 was 5.93 years (range 2–15 years), in group 2 was 5.8 (range 2–14 years) and in group 3, 7.6 years (range 2–14 years). In all, 32.1% of children in group 1 had spastic tetraplegia whereas in group 2, spastic diplegia was the commonest type of CP (34.3%) (Table 1). A history of hypoxic ischemic encephalopathy (HIE) was present in 60.7 and 60% in groups 1 and 2, respectively. Gestational age at birth varied in the two groups in that 85.7% of children in group 1 were born at term as compared to 54.3% of children with CP in group 2. A positive family history of seizures was present in four and two children, respectively, in groups 1 and 3.

Table 1: Incidence of epilepsy in various types of CP.

Type of CP	CP with seizures	CP (control)
Spastic diplegia	15	12
Spastic tetraplegia	18	6
Spastic hemiplegia	5	6
Extrapyramidal	0	3
Ataxic	9	5
Mixed	9	3
Total	56	35

Nature of epilepsy

Thirty-six children with CP presented with generalized tonic, clonic or tonic clonic seizures; however, EEG studies proved that a majority of these had partial epilepsy with secondary generalization. According to the ILAE revised classification of epileptic seizures (1981) 18 children (32.1%) had generalized tonic/tonic clonic or clonic seizures, 22 (39.3%) had partial epilepsy, 8 (14.3%) had myoclonic epilepsy and 3 (5.4%) had infantile spasms. Three children had atonic and two had mixed type of epilepsy (Table 2). Table 3 shows the type of CP and the seizure pattern. In children with epilepsy without CP (group 3), partial seizures were far more common at presentation and were present in 28 children (56%).

Age of seizure onset

Epilepsy in children with CP was associated with an earlier onset of seizures than in controls; 44 children (78.6%) in the CP group developed seizures in the first

Table 2: Types of epilepsy in CP and control patients.

Epilepsy	Group 1 ($n = 56$)	Group 3 ($n = 50$)
Generalized tonic/tonic clonic/clonic	18	10
Absence	0	4
Myoclonic	8	3
Atonic	3	0
Infantile spasms	3	2
Lennox Gastaut syndrome	0	2
Partial simple/complex	22	28
Polymorphic	2	1

Table 3: Type of CP versus seizure pattern cross tabulation.

Type of CP	Generalized	Partial	Myoclonic	Infantile spasm	Atonic	Mixed (more than one type)	Total
Spastic diplegia	5	6	2	1	1		15
Spastic tetraplegia	6	6	3	1	1	1	18
Spastic hemiplegia	1	4					5
Cerebellar	2	2	2	1	1	1	9
Mixed	4	4	1				9
Total	18	22	8	3	3	2	56

year of life compared with 2 (4.1%) in the controls. Neonatal seizures were present in 42.9% in group 1 and in 28.6% in group 2; there were no cases of neonatal seizures in group 3. A history of status epilepticus was present in 19 children (33.9%) in group 1 and two children (4%) in group 3 (Table 3). The inter-ictal EEG was abnormal in 49 (87.5%) and 45 (90%) children in groups 1 and 3, respectively. Interestingly, hypsarrhythmia was seen in two children (3.6%) in group 1 and five children (10%) in group 3.

Brain imaging studies

CT scan and/or MRI was performed on all children in the groups 1 and 2. Apart from three (5.4%) children in group 1 and one (2.9%) child in group 2, who showed normal imaging all the remaining children in these groups showed abnormalities. Significant brain volume reduction, periventricular leucomalacia (PVL), basal ganglia changes, multicystic encephalopathy and schizencephaly were the major abnormalities seen (Table 4). In contrast, out of the 46 children in group 3 in whom brain imaging was done, 37 children (80.4%) had normal images. Focal abnormalities such as infarction, focal atrophy, cerebellar atrophy and mesial temporal sclerosis was seen in one each. Interestingly three children in group 3 with seizures only had mild PVL with no associated neurological deficits.

Use of antiepileptic drugs

Effective treatment of seizures in CP in group 1 was more difficult with 37 children (66.1%) needing poly therapy with more than 1 antiepileptic drug. In fact 16 children were on 3 or more drugs and 5 out of 18 children with tetraplegia needed 4 or more anticonvulsants. In the control group of children with epilepsy, 35 children (70%) were on monotherapy; only 3 children in this group were on more than 3 drugs for seizure control. Good seizure control was seen in 12 (21.4%) children with CP and 34 (68%) children without CP; poor seizure control was seen in 20 (35.7%) and 3 (6%) children in these two groups, respectively. Forty-seven (83.9%) children in group 1 and 35 (42.7%) in group 3 were still on medication 18 months after starting the therapy. It is interesting to note that 15 out of 18 children (83.3%) with spastic tetraplegia and epilepsy were on polytherapy as against 6 out of 15 children (40%) with spastic diplegia; only 1 child with spastic tetraplegia with epilepsy was considered to have a good control of his seizures. Five out of 15 children with spastic diplegia had good control of seizures.

DISCUSSION

Epilepsy is more common in certain types of CP than others with tetraplegic variety having the highest

Table 4: Brain imaging findings among three groups.

Findings	CP with seizures ($n = 56$)	CP ($n = 35$)	Epilepsy ($n = 46$)	P-value[a] significance
Normal	3 (5.4%)	1 (2.9%)	37 (87.4%)	
Brain atrophy	18 (32.1%)	3 (8.6%)	1 (2.2%)	$P < 0.001$
PVL	8 (14.3%)	11 (31.4%)	3 (6.5%)	$P < 0.01$
Basal ganglia changes	–	7 (20%)		–
Multicystic encephalopathy	8 (14.3%)	5 (14.3%)		NS
Porencephaly/infarction	4 (7.1%)	5 (14.3%)	1 (2.2%)	NS
Schizencephaly	6 (10.7%)			–
Cerebellar atrophy	2 (3.6%)	1 (2.9%)	1 (2.2%)	NS
Miscellaneous	2 (3.6%)			–
Mesial temporal sclerosis			1 (2.2%)	–

NS: not significant.
[a] Chi-square test was performed.

incidence of seizures, ranging from 50 to 94%, which in turn, might be a reflection of the severity of damage to the brain[6,7]. In the current study, spastic tetraplegia was the commonest type of CP complicated by seizures. Spastic diplegia was the commonest type of CP in the control group of CP without seizures. Both partial and generalized epilepsies were seen in equal proportions in spastic diplegia. Gurses *et al.* reported that 47% of children with periventricular leucomalacia (PVL) had epilepsy, 78% of which was intractable[8] and PVL was mostly associated with spastic diplegia. There were no children with extra pyramidal type of CP who developed seizures. In the hemiplegic variety, partial seizures were more common representing a unilateral, focal lesion, such as infarct or a porencephaly. Other studies have found a similar high incidence of partial seizures in this variety of CP ranging from 69 to 73%[1,9]. In the pure cerebellar type of CP, seizures are believed to be uncommon[6,10] but in the present study there were 9 children with seizures within this group. Classification of the type of epilepsy is often difficult in children with CP for many reasons; firstly the partial onset prior to generalization may not be apparent or witnessed; impairment of consciousness during ictal period may be difficult to detect in a child with severe handicaps; lastly, the differentiation between myoclonic, brief tonic and atonic seizures could be difficult without ictal EEG or video EEG[2].

The increased risk of epilepsy in CP is believed to be linked to genetic and perinatal factors[6]. First-degree relatives of children with CP and seizures have been reported to have an increased incidence of seizures[3]. Among the perinatal factors, structural and developmental defects of the brain, chromosomal defects, intrauterine infections and hypoxic ischemic brain injuries are the more obvious causes that may result in seizures. Brain imaging may provide a clue regarding the timing and nature of the brain insult in these children[11].

In the present cohort, a wide variety of abnormal images were seen (Table 4) indicating a possible prenatal and perinatal factor as the cause for the brain damage. In 94.6% of the children in group 1 there were significant radiological abnormalities with 32% showing significant brain volume reduction without any other obvious pathology. A similar pattern was noted in children with CP but no seizures with 97.1% of those studied showing significant brain pathology. Presence of significant brain volume reduction and schizencephaly were the only radiological signs that were more common in group 1 and basal ganglia changes were present solely in group 2. It is difficult to explain why the children in group 2 did not have seizures in spite of significant radiological abnormalities. One possibility is that seizures may occasionally be missed in children with severe handicaps. If EEG recording is routinely performed on this group of children with CP with no seizures, presence of epileptic discharges may be evident indicating occult or missed seizures.

In the present 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 incidence of neonatal seizures in this group of children as compared with the other two control groups (Table 5). This possibly reflects a more severe grade of HIE. In group 1, 79% of children developed their first seizure in the first year of life and only 9% had their first seizure after their 5th birthday. In the previous studies, Aksu found that the seizures started within 2 years in 50% of the children[3]. 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. In spite of adequate drug therapy, poor seizure control, defined as daily or weekly recurrences in spite of adequate serum levels of appropriately used drugs, was seen in 20 (35.7%) children in group 1, as against 3 (6%) of children with seizures without CP. Good seizure control could be observed in only 12 (21.4%) of children in group 1

Table 5: Factors associated with CP and epilepsy.

Variable	Group 1 (CP + seizures) ($n = 56$)	Group 2 (CP) ($n = 35$)	Group 3 (seizures) ($n = 50$)	*P*-value[a] significance
Neonatal seizures	24 (42.9%)	10 (28.6%)	0	NS
H/O HIE	34 (60.7%)	21 (60%)	0	NS
Developmental delay	55 (98.2%)	31 (88.6%)	10 (20%)	$P < 0.001$
Status epilepticus	19 (33.9%)	0	2 (4.0%)	$P < 0.001$
Abnormalities on brain imaging	53 (94.6%)	35 (97.1%)	9 (19.6%)	$P < 0.001$
Need to use two or more AED	37 (66.0%)	–	15 (30%)	$P < 0.001$
Good seizure control[b]	12 (21.4%)	–	34 (68%)	$P < 0.001$

NS: not significant.
[a] Chi-square test was performed; [b] Seizure-free period of 12 months.

as against 34 (68%) in group 3. In particular, children with spastic tetraplegia more often needed polytherapy with 9 out of 18 children requiring 3 or more anticonvulsants and 5 needing 4 or more drugs despite which some had refractory seizures. This may be due to the more extensive brain pathology seen on brain imaging in this group of children. It is also possible that certain genetic factors, as yet unidentified, may play a role in the pathogenesis of seizures in children with CP, particularly in the tetraplegic variety. In this study, the relapse rate could not be determined since 47 children in group 1 were on antiepileptic drugs during the period of the study and in 9 the drugs had been stopped for less than 6 months. In the series reported by Zafeiriou *et al*. 13.4% of children with CP and epilepsy relapsed after a 3-year seizure-free period and subsequent discontinuation of antiepileptic drugs[12]. Generally it is believed that children with diplegia have a lower relapse rate as compared to those with hemiplegia or quadriplegia[2, 4, 6, 8].

When we compare the two groups of children with CP with seizures and those without seizures, the following variables seem to have an increased association with the seizure group: positive history of HIE, term delivery, a history of neonatal seizures, spastic tetraplegic variety of CP and presence of schizencephaly on brain imaging. For a good seizure control/outcome, the following three variables seem to be significant: absence of neonatal seizures, age of onset after 1 year and absence of a significant focal or multicystic brain damage or a cerebral malformation on brain imaging. Further studies looking in to possible genetic and early prenatal factors may lead to better understanding of the cause of epilepsy in CP.

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