RESEARCH ARTICLE

# RISK FACTORS AND PROGNOSIS OF EPILEPSY IN CHILDREN WITH HEMIPARETIC CEREBRAL PALSY

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## Abstract

### Objective

Epilepsy is reported in 15-90% of the children with Cerebral Palsy (CP) but its clinical course is not well defined.
We conducted a retrospective study on children with hemiparetic CP who were referred to Pediatric Neurology Department of Mofid Hospital. The aim of our study was to evaluate the risk factors and prognosis of epilepsy in children with hemiparetic CP.

### Materials & Methods

We evaluated 64 children with hemiparetic CP who were referred to Pediatric Neurology Department of Mofid Hospital between 2006 and 2008.
According to our protocol, patients were divided into two groups: 34 children in the case group (hemiparetic patients with epilepsy) and 30 children in the control group (hemiparetic patients without epilepsy).

### Results

Prenatal, perinatal and postnatal events, maternal age at the time of delivery, socioeconomic status of the family, familial history of epilepsy, neuroimaging findings, side of the hemiparesia and age at diagnosis of hemiparesis were not considered as risk factors for epilepsy in hemiparetic children, but microcephaly, severity of hemiparetic CP and mental retardation were significantly associated with an increased risk of epilepsy in children with hemiparetic CP.

### Conclusion

Our study showed that microcephaly, severity of hemiparesis and mental retardation were risk factors for developing epilepsy in children with hemiparetic CP; furthermore, they had negative effects on rehabilitation outcome in these patients.

**Keyword:** Hemiparetic Cerebral Palsy, Epilepsy, Children, Microcephaly, Mental Retardation

## Introduction

Cerebral Palsy (CP) is a term that defines a group of non – progressive syndromes of motor impairment secondary to lesions or anomalies of the brain, arising in the early stages of its development (1). Cerebral palsy has been subdivided into various entities based on the clinical presentation:
- Spastic cerebral palsy:
a) Spastic quadriparesis
b) Spastic diplegia

c)Spastic hemiparesis
- Extrapyramidal cerebral palsy
- Hypotonic (atonic) cerebral palsy
-Cerebellar cerebral palsy
-Mixed type cerebral palsy

Spastic hemiparesis is characterized by a unilateral paresis that almost always affects the upper extremities more than the lower ones. It is associated with different levels of spasticity and flexion contractures of the affected limbs.

The incidence of CP ranges from 1.5 to 2.5 per 1000 live births (2). The incidence of hemiparetic CP was reported to be between 0.41 and 0.79 per 1000 live births by Cioni (3). Grether et al. included 19% of children with cerebral palsy in their series (4).

One limited study by Karimzadeh in Iran showed diplegic CP as the frequent type of CP in Iran (5).

More than one half of the hemiparetic patients develop Seizures.

In order to determine the risk factors of epilepsy in children with hemiparetic CP, the outcome of children with hemiparetic CP and the affecting factors, we conducted a retrospective study on epilepsy in a hospital – based series of children with this type of CP.

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences.

Prior to the study, all parents signed an informed written consent.

## Materials & Methods

We conducted a cohort study on hemiparetic children at Mofid Children's Hospital between January 2006 and January 2008 in Tehran, Iran. The subjects were children aged 2-10 years with the diagnosis of hemiparetic CP attending the department of child neurology. Patients had to meet the following criteria to be included in our investigation: (1) congenital hemiparetic CP, (2) age between 2 and 10 years.

Patients were divided into two groups: 34 hemiparetic patients with epilepsy in the case group and 30 hemiparetic CP patients without epilepsy in the control group. The parents were interviewed using a questionnaire regarding prenatal, perinatal and postnatal periods, socioeconomic status of the family, and the type of seizures and used antiepileptic drugs (AEDs) (the latter two in the case group). Then, a detailed neurologic examination was performed by a pediatric neurologist and IQ testing was done by a psychologist. Finally, patients were referred to a rehabilitation center.

We tried to use an academic rehabilitation center for their qualitative methods and then we followed the patients for two years.

**Definitions**

1- The term hemiplegic cerebral palsy comprises several pathological entities that result in limb spasticity and weakness on one side of the body (6).

2- Epilepsy was defined as a separate occurrence of two or more apparently unprovoked seizures (7). The seizure outcome was defined as good if the patient was seizure-free for more than 2 years. Intractable epilepsy was defined as the occurrence of two episodes of seizure per month in spite of appropriate drug therapy with two or more conventional AEDs like Phenobarbital, Valproic acid and Carbamazepine (7).

3- Prematurity was defined as a gestational age of less than 37 weeks from the first day of the last menstrual period.

4- Prenatal pathology, including maternal hypertension, maternal vaginal bleeding and maternal hyperglycemia during pregnancy, was considered.

5- The diagnosis of mental abnormality was based on clinical assessments, supplemented by standard tests.

6- The severity of hemiplegia was assessed based on walking delay and walking ability before rehabilitation.

- Severe: If independent walking started after 15 months of age or the patient was still unable to walk and both upper and lower limbs were paretic.
- Mild: If independent walking started before 15 months of age and only the upper limbs were paretic.

7- Icterus: History of first day jaundice or later jaundice with a total bilirubin equal or more than 10 mg/dl.

8- Asphyxia: History of using supplemental oxygen within seven days after brith.

Children with epilepsy and hemiparetic CP were compared with hemiparetic CP patients without epilepsy.

## Results

### Analysis

The differences between the groups were evaluated with parametric t-test and nonparametric statistical tests: Fishers Exact test or chi-square test. All P values were two– tailed. Statistical significance was defined as $p<0.05$.

### Findings

Mental assessment (IQ test) and rehabilitation was administered for 74 children with hemiparetic CP who entered the first phase of the study. Ten children did not continue rehabilitation and were therefore omitted from the study. Age, sex, birth weight, number of maternal deliveries, mode of delivery and gestational age were recorded.

Prenatal and perinatal pathologies (maternal hypertension or vaginal bleeding during pregnancy and maternal age at the delivery time), socioeconomic status of the family (father's education and owning or renting the residence), icterus and asphyxia, cardiac anomaly, familial history of epilepsy, MRI findings, the affected side and age at time of diagnosing hemiparesis were not related to the development of epilepsy (Table. 1,2,3).

Microcephaly was significantly associated with an increased risk of epilepsy in children with hemiparetic CP (Table 1) The severity of hemiparetic CP and mental retardation were also associated with epilepsy.

The study group consisted of 34 patients with hemiparetic CP who developed epilepsy with an age range of 2 to 10 years. Neonatal seizures occurred in eight (23%) children with hemiparetic CP and epilepsy.

Forty-four percent (44%) of the hemiparetic patients with epilepsy developed epilepsy in their first year of life.

The mean age at onset of epilepsy was 3.4±2.17 years in hemiparetic children. One patient had status epilepticus. Epileptic attacks included generalized tonic clonic (GTC) in seventeen children, partial seizures with secondary generalization in four children, partial seizures in six children, myoclonic seizures in four children and mixed type seizures (lennox-Gastaut syndrome) in three children. The type of GTC was the predominant type of convulsions.

MRI of brain was performed in all 64 children with hemiparetic CP and at least one abnormality was detected in 21 (61.8%) patients in the case group and 12 (40%) patients in the control group; however, the difference between the two groups was not significant ($P = 0.06$) (table 1).

MRI findings in CP patients with epilepsy included cerebral atrophy in six patients, periventricular leukomalacia in four, focal infarction in seven, pachygyria in three, schizencephaly in two, and porencephaly in two patients while thirteen MRIs were normal. In hemiparetic CP patients without epilepsy, the following neuro-radiologic abnormalities were present: cerebral atrophy in three patients, periventricular leukomalacia in three and pachygyria in one patient while eighteen MRIs were normal.

Thirty – two patients in the CP group with epilepsy were on antiepileptic drugs at the time of this study.

AEDs were discontinued in only two children with CP. Monotherapy was done in nine patients. Intractable seizure was common in children whose seizures began during the first year of life. The seizure outcome in our patients showed that 8 patients (23%) had intractable epilepsy; therefore, twenty-six patients (77%) in the CP group had well controlled seizures. Among those children with well controlled seizures, AEDs were discontinued in only two patients (5%). None of the children with Lennox-Gastaut syndrome achieved a seizure free period of more than 1 year. Although rehabilitation in hemiparetic patients with epilepsy was performed for at least two years, these patients did not respond well to rehabilitation compared to the control group (Occupational Therapy or Physio herapy) ($P <0.008$) (Table 2).

**Table 1:** Risk Factors of epilepsy in Hemiparetic CP patients

| Variables | | With epilepsy (N=34) | Without epilepsy (N=30) | P-Value |
|---|---|---|---|---|
| **Age (years)** | (Mean± SD) | 6.32 ±3.24 | 5.42±2.98 | Ns (0.25) |
| **Sex** | male | 20 | 16 | Ns (0.4) |
| | female | 14 | 14 | |
| **Birth weight (gr)** | (mean ±SD) | 2641±857 | 2486±620 | Ns (0.4) |
| **Gestational age (weeks)** | | 37 | 37 | Ns (0.8) |
| **Icterus** | Yes (bili >10 more than 10th day) | 9 | 8 | Ns (0.9) |
| **Asphyxia** | Yes | 7 | 3 | Ns (0.4) |
| | No | 27 | 27 | |
| **Cardiac anomaly** | | 3 | 0 | Ns (0.1) |
| **MRI findings** | Normal | 13 | 18 | Ns (0.6) |
| | Abnormal | 21 | 12 | |
| **IQ** | Mean ±SD | 80± 23.77 | 103.9±21.13 | 0.0001 |
| **Microcephaly** | | 7 | 2 | 0.0001 |
| **Family history of epilepsy** | | 4 | 1 | Ns (0.2) |
| **Walking time (month)** | Mean ±SD | 19.92±9.08 | 15.56±6.35 | (0.04) |
| **Age at diagnosing hemiparesis (month)** | Mean ±SD | 14.61±6.20 | 15.66±5.44 | Ns (0.4) |
| **Hemiparetic side** | Right | 18 | 18 | Ns |
| | Left | 16 | 12 | |
| **Hemiparetic limb** | Hand or foot | 17 | 24 | 0.025 |
| | Hand or foot | 17 | 6 | |
| **Father's education** | Primary or secondary school | 8 | 5 | Ns (0.7) |
| | High school | 18 | 17 | |
| | University | 8 | 8 | |
| **Residence** | Owned | 10 | 16 | NS (0.4) |
| | Rented | 24 | 14 | |

## Discussion

In our study, gestational age and history of delivery did not differ significantly between the hemiparetic groups. Gestational age and birth weight were almost similar in both groups, suggesting that these factors had no significant effect on the incidence of epilepsy in hemiparetic patients.

In the Swedish series of Hagberg et al., spastic hemiparesis was seen in 44% of term infants with cerebral palsy, 9% of premature infants with cerebral palsy and a gestational age of less than 28 week, 10% of the infants with a gestational age of 28 to 31 weeks, and 32% of the infants with a gestational age of 32 to 36 weeks (8).

Cazauvielh noted the correlation between congenital hemiparesis and cerebral abnormalities in 1972 and an antecedent history of the abnormalities of labor and delivery was proposed by McNutt, Fred and Rie (9, 10). Since then, it became clear that the etiology of hemiparetic CP was multifactorial and that both morphogenetic and classic lesions were responsible, but the incidence of abnormal events in pregnancy and delivery in this from of cerebral palsy was found to be relatively low (10).

Our study showed that the mean age at onset of epilepsy was 3.4±2.1 years, with the first seizure occurring during the first year of life in 44% of the hemiparetic patients with epilepsy.

Forty-seven percent of the patients in the hemiparetic CP group developed epilepsy in their first year of life in a report by Jacobs (11).

Neonatal seizures were observed in eight patients. The presence of neonatal seizures was considered to be a risk factor for subsequent development of neurologic disabilities (mental retardation, motor delay and epilepsy) (12). Kwong et al. noted neonatal seizures in 19% of the children with CP and epilepsy (13). Levene reported that neonatal seizures had adverse effects on neurodevelopmental progression and might predispose patients to cognitive, behavioral, or epileptic complications later in life (14).

We observed generalized seizures more frequently in our epileptic hemiparetic patients; Aksu and Delgado et al. reported that focal or secondarily generalized seizures were common in children with hemiparetic CP and primary generalized epilepsies were less frequent (15, 16).

In contrast, Kwong et al demonstrated that generalized epilepsies were less frequently observed in patients with hemiparetic CP and polymorphic seizure types were more common (13).

Polytherapy was used in 73% of our study group; however, lower percentages were reported by Kwong et al. (about 30%) (13) and Lulak W. (about 45%) (17).

We had two patients with seizure remission. The seizure remission rate in children with hemiparetic CP is still not fully defined. Jacobs noted that children with tetraplegia and extrapyramidal forms of CP stood a better chance of remission (13). Delgado et al. also observed that most patients with hemiparetic CP and epilepsy did not have a seizure remission period of two years or more (16). Cohen et al. noted that in hemiparetic patients who had seizures during the neonatal period, the likelihood of recurrence was about 100% (18).

Early prediction of intractable epilepsy would be valuable because rapid identification of patients who are at highest risk of being intractable would allow physicians to consider them earlier for treatment with the recently approved medications and other surgical and nonsurgical treatments (19).

The present study demonstrated that epilepsy in children with CP was associated with a relatively poor prognosis. Only two epileptic children with hemiparetic CP were seizure free for more than 2 years. About 16% and 12% of the epileptic children with CP were seizure free for more than 2 years in studies conducted by Kwong et al (13) and Aksu (15).

We believe that seizure types play an important role in determining the prognosis of seizure in hemiparetic CP patients since we noted that myoclonic seizures were associated with a poor prognosis regarding epilepsy in hemiparetic CP patients.

According to our findings, hemiparetic patients with epilepsy did not show a good outcome after rehabilitation ($P < 0.008$, Table 2); however, Blicher and Nielsen noted that rehabilitation outcome did not correlate with epilepsy (20).

**Table 2:** Rehabilitation and its outcome in hemiparetic CP patients

| Variables | | With epilepsy (N=34) | Without epilepsy (N=30) | P-Value |
|---|---|---|---|---|
| **Rehab type** | OT | 14 | 16 | Ns (0.34) |
| | PT | 5 | 6 | |
| | OT and PT | 15 | 8 | |
| **Mean age at onset of Rehab (months)** | Mean ± SD | 26.97±18.99 | 24.06±8.97 | Ns (0.44) |
| **Rehab duration (months)** | Means ± SD | 24..51±18.07 | 15.86±12.16 | 0.031 |
| **Hand movement before Rehab** | Object holding | 21 | 20 | Ns (0.44) |
| | No object holding | 13 | 10 | |
| **Hand movement after Rehab** | No object holding | 8 | 0 | 0.005 |
| | Object holding | 26 | 30 | |
| **Walking before Rehab** | No walking | 8 | 1 | 0.02 |
| | Walking | 26 | 29 | |
| **Walking after Rehab** | No walking | 8 | 0 | 0.008 |

OT:Occupational Therapy, PT:Physiotherapy

The present study documented a significant difference in Intelligence Quotient between hemiparetic children with epilepsy and those without it ($P < 0.0001$).

Vargha-Khadem et al. reported that in patients with hemiplegia, the presence of epilepsy was clearly associated with more severe cognitive difficulties (21). In the series of Cocioni et al., mental retardation was documented in 30% of the hemiparetic patients who sustained a first trimester insult and in 18% of the patients with a perinatal injury (3).

We demonstrated a higher proportion of MRI abnormalities in children with hemiparetic CP and epilepsy compared to the control group. A study conducted by Sebil et al. demonstrated cranial imaging abnormalities in 74.2% of the epileptic and 48.8% of the non-epileptic CP patients (22). Although we found no significant difference between the two groups, the epileptic group revealed more structural abnormalities (Table 1). In contrast, Kwong et al detected MRI abnormalities in 74% of the CP patients with epilepsy and 77% of the CP patients without epilepsy (13). In a series of 91 cases reported by Cioni et al., first trimester lesions, including focal cortical dysplasia, migrational disorders, and schizencephaly, were seen in 14% of the cases (3).

In our survey, the severity of motor involvement in the epileptic group was higher than the non-epileptic group which was in accordance with the higher incidence of motor involvement in epileptic patients found by Bruck et al (23).

Our study showed that the right side of the body was involved more than the left side [50% (18) in the case group and 60% (16) in the control group]. Just the same, the incidence of right sided involvement was reported to be 59% in a study by Ingram (24).

We did not find any correlation between socioeconomic status and epilepsy in hemiparetic patients; however, Elwyn Chomba et al. showed that the incidence of epilepsy was high in patients of significantly lower socioeconomic status (25).

We also found no significant correlation between epilepsy and maternal factors

[(maternal hypertension or vaginal bleeding during pregnancy and maternal age at the delivery time (Table 3)], icterus and asphyxia, cardiac anomaly, the affected side and age at diagnosis.

Most of the studies on the outcome of childhood epilepsy have different proportion of CP types so the results are often different (1, 2, 5, and 6) while our study, with the homogenous group of hemiparetic CP patients, has more important proprietary to identify the outcome of epilepsy.

We are aware of the limitations of our study. One limitation was that our patients needed a long period of rehabilitation. On the other hand, rehabilitation methods in Iran are very variable and directly dependent on the therapist; therefore, there is need for more in-depth studies to evaluate different types of rehabilitation methods in children with cerebral palsy.

**Table 3:** Maternal factors in hemiparetic CP patients

| **Variables** | | with epilepsy (N=34) | Without epilepsy (N=30) | **P-Value** |
|---|---|---|---|---|
| **Delivery** | Normal Vaginal delivery | 18 | 19 | Ns (0.8 ) |
| | Cesarean section | 16 | 11 | |
| **Maternal age at the delivery time** | (mean ± SD) | 28,8±5.4 | 27.6±5.2 | Ns (0.5) |
| **Maternal hypertension during pregnancy** | | 2 | 1 | Ns (0.5) |
| **Vaginal bleeding during pregnancy** | | 2 | 1 | Ns (0.5) |
| **Number of deliveries** | Mean ±SD | 1.7±1.05 | 1.90± 1.2 | Ns (0.5) |

**In conclusion,**Based on the results of this study, microcephaly, severity of hemiparesis and mental retardation were risk factors for developing epilepsy in children with hemiplegic cerebral palsy.

Our findings revealed that epilepsy had negative effects on rehabilitation outcome in these patients.

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