Korean Journal of Pediatrics Vol. 53, No. 1, 2010
DOI : 10.3345/kjp.2010.53.1.80
■ Original article : Clinical study ■

# Long-term outcomes of infantile spasms

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= Abstract =

**Purpose :** The aims of this study were to investigate the long-term outcomes in children with infantile spasms (IS) and to identify the prognostic factors influencing their neurodevelopment.
**Methods :** We retrospectively evaluated seventy two children over five years old who were treated for IS at Asan Medical Center, Seoul, Korea, between 1994 and 2007. Forty-three children were contacted by telephone or medical follow-up to assess their current neurodevelopmental status. Multiple logistic regression was used to calculate odds ratios (ORs) and 95% confidence interval (95% CIs) of risk factors for unfavorable outcomes.
**Results :** The mean follow-up duration for these 43 children was 7.2±1.5 years (range, 4.5 to 13.0 years). Of these, 13 (30.2%) had cryptogenic and 30 (69.8%) had symptomatic IS. Eleven (25.6%) children were initially treated with adrenocorticotrophic hormone (ACTH) therapy, with a mean treatment lag of 1.3±1.9 months (range; 0.1 to 7.0 months). Eighteen (41.8%) children clinically responded to initial treatment, as shown by EEG response. Overall, 22 (51.2%) children had at least moderate neurodevelopmental disorders and 2 (4.8%) died. In univariate analysis, etiology (symptomatic) and poor electroclinical response to initial treatment were related to long-term unfavorable outcomes. In multivariate analysis, response to primary treatment was the sole significant independent risk factor with a high OR.
**Conclusion :** Overall prognosis of children with IS was poor. Electroclinical non-responsiveness to initial treatment was related to unfavorable long-term outcomes, indicating that initial control of seizures may be important in reducing the likelihood of poor neurodevelopment. **(Korean J Pediatr 2010;53:80-84)**

**Key Words :** Infantile spasm, Long-term outcome, Prognostic factor

## Introduction

Infantile spasm (IS), one of the most common forms of epileptic encephalopathy, is a childhood syndrome characterized by specific epileptic seizures and a specific electroencephalography (EEG) pattern, as well as being one of the major causes of acquired mental retardation and neurodevelopmental disorders in early childhood[1, 2]. It is conventional thought that persistent spasm and hyperarrhythmia inhibit the normal development and growth of the brain, predisposing toward neurodevelopmental delays even after the cessation of seizures[3]. Accordingly, early and initial control of spasms and abnormal EEG waves may be the cornerstone of IS treatment to prevent cognitive and psychosocial dysfunction, while resistance to treatment and transition to other types of seizure have been clinically problematic[3, 4].

Many studies have investigated the long-term outcomes in patients with IS and the factors prognostic of poor neurodevelopment[3-7]. Underlying etiology, pre-existing developmental delay, response to initial treatment, and treatment lag (lead time from apparent onset to treatment initiation) have been cited as the major risk factors for poor neurodevelopment and/or mental retardation[3-7]. The natural history of IS, however, has not been determined and most factors prognostic of poor outcome have been identified from retrospective and heterogeneous studies, including different populations and different treatment regimens [6]. In 2001, the West Delphi Group[8] proposed a consensus

Received : 15 July 2009, Revised : 18 September 2009
Accepted : 26 October 2009
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statement for the standardization of IS definitions and outcome measures. Here, we analyzed the long-term neurodevelopmental outcomes in children with IS to investigate factors prognostic of unfavorable outcomes.

## Materials and methods

The study population included 76 children with IS, aged >5 years at the time of data collection, treated at Asan Medical Center, Seoul, Korea, between January 1994 and January 2007. The medical records and computerized databases of these children were reviewed retrospectively. The terminology and selection of variables were based on study guidelines proposed by the West Delphi Group[8]. The following characteristics were selected: age at onset (corrected age for prematurity), sex, seizure pattern, treatment lag, EEG pattern, developmental delay at the time of diagnosis, etiology (cryptogenic vs. symptomatic), and primary clinical and electroclinical outcomes after initial treatment (cessation of spasms and EEG response for 1 month after initiation of treatment). EEG reports were reviewed by experienced pediatric neurologists of Asan Medical Center, and specific etiologies in the symptomatic group were identified according to ICD-10[9].

Long-term outcomes included death and unfavorable neurodevelopment (i.e. moderate to severe mental retardation or neurodevelopmental disorder), which were assessed using questionnaires and medical records. The questionnaires included questions related to academic underachievement, behavioral and/or emotional difficulties, physical restrictions or degree of self-care, and concerns about visual and auditory disturbances[10]. Multiple logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for risk factors for unfavorable outcomes, using SPSS software (SPSS for Windows, Release 14.0; SPSS Inc., Chicago, IL, USA). A $P$ value less than 0.05 was considered statistically significant.

## Results

Of the 76 children with IS, 43 could be contacted by hospital visit or telephone for assessment of their neurodevelopmental status. The mean age of these 43 children at the time of data collection was 9.6±2.4 years (range, 5.0 to 13.2 years) and the mean follow-up time was 7.2±1.5 years (range, 4.5 to 13.0 years). Table 1 shows the etiologic classification of the population. Of these 43 children, 13 (30.2%) had cryptogenic and 30 (69.8%) had symptomatic IS. Of the 30 children with symptomatic IS, 14 (46.7%) had perinatal disorders, 13 (43.3%) had congenital abnormalities, 2 (6.7%) had nervous system disorders, and 1 (3.3%) had a neoplasm.

Table 2 shows the characteristics of the study population. The mean age at seizure onset was 5.0±3.8 months (range, 0.1 to 22.0 months), with 11 (25.6%) having early onset (<3 months), 30 (69.8%) having classic onset (≥3 and ≤12 months), and 2 (4.7%) having late onset (>12 months) IS. Thirty five (81.4%) children had brief symmetric contractions of the neck, trunk, and extremities, which constitute the typical seizure pattern in IS. Eleven (25.6%) children had pre-existing developmental delays. Eleven (25.6%) children were initially treated with adrenocorticotrophic hormone (ACTH) therapy. The mean treatment lag was 1.3±1.9 months (range, 0.1 to 7.0 months). Eighteen (41.8%) children responded to initial treatment and 18 (41.8%) had EEG responses. Overall, 31 (72.1%) children had at least mild neurodevelopmental disorders, with 9 (20.9%) having mild, 8 (18.6%) having moderate, and 12 (27.9%) having severe neurodevelopment disorders.

**Table 1.** Etiologic Classification of Infantile Spasms

| | Number (n=43) (%) |
|---|---|
| Cryptogenic | 13 ( 30.2) |
| Symptomatic | 30 ( 69.8) |
| Perinatal | 14 ( 32.6) |
| Periventricular leukomalacia | 9 ( 64.4) |
| Hypoxic ischemic encephalopathy | 3 ( 21.4) |
| Intracranial hemorrhage | 1 ( 7.7) |
| Subdural hygroma | 1 ( 7.7) |
| Congenital | 13 ( 30.2) |
| Lissencephaly | 2 ( 15.4) |
| Tuberous sclerosis | 1 ( 7.7) |
| Brain atrophy | 3 ( 23.0) |
| Neurofibromatosis | 1 ( 7.7) |
| Focal cortical dysplasia | 1 ( 7.7) |
| Noonan syndrome | 1 ( 7.7) |
| Leukodystrophy | 1 ( 7.7) |
| Congenital cytomegalovirus | 1 ( 7.7) |
| Infection | 1 ( 7.7) |
| Heteropia | 1 ( 7.7) |
| Nervous system | 2 ( 4.7) |
| Cerebral abscess | 1 ( 50.0) |
| Meningitis | 1 ( 50.0) |
| Neoplasm | 1 ( 2.3) |
| Hypothalamic harmatoma | 1 (100.0) |

In addition, 2 (4.8%) died.

In univariate analysis, etiology (symptomatic) ($P$=0.023, OR=2.09, 95% CI=0.55 to 7.91) and absence of primary electroclinical outcome (cessation of seizure or EEG response) ($P$=0.005, OR=25.14, 95% CI=1.46 to 234.17) were significantly related to unfavorable outcomes (Table 3). In multivariate analysis, response to primary treatment was the sole significant independent risk factor for unfavorable outcome, with a high OR ($P$=0.023, OR=20.47, 95% CI=1.93 to 160.98).

## Discussion

Since the first description of IS in 1841[11], this disorder has been of great interest to clinicians because of its association with poor long-term neurodevelopment. IS is a rare form of epileptic encephalopathy characterized by specific epileptic seizures and specific EEG patterns, known as hypsarrhythmia[12]. IS is rare with a frequency of 0.16 to 0.42 per 1,000 live births[13] and accounting for 2-3% of children with childhood seizures[14]. In Korea, however, the incidence of IS in the general population is not yet known. Approximately 90% of children with IS present with convulsive features during the first year of life, with a peak between 4 to 8 months. Characteristic IS seizures, described as "Salaam attacks", tend to appear suddenly in clusters of brief symmetric contractions of the neck, trunk, and extremities, while the patient is drowsy or immediately upon awakening[2]. Hypsarrhythmia consists of chaotic patterns of high voltage spikes, bilateral asynchrony, and slow-wave activity[2, 12-14]. EEG patterns characteristic of IS are more likely to occur during early stages of IS or in younger patients[12-14]. ACTH has been shown to resolve spasms faster than vigabatrin, although evidence of long-term benefits of ACTH in the prevention of neurodevelopmental disorders has been insufficient in a recent Cochrane study[15].

IS is frequently characterized by unfavorable neurodevelopmental outcomes, treatment resistance, frequent relapse, and transition to other forms of seizures, with 80% to 90% of children with IS developing mental retardation as adults[16]. A study of 147 children with IS showed that only 36% were seizure free, whereas 18% presented with Lennox-Gastaut syndrome, and 76% had moderate to severe mental retardation (IQ less than 68)[3]. In most patients, the IQ of adults was similar to that determined at a mean age of 8 years, whereas IQ level decreased among

**Table 2.** Characteristics of Total Study Population and Unfavorable Outcomes of Children with Infantile Spasms

| | Number (n=43) (%) |
|---|---|
| Characteristics at time of diagnosis | |
| Age at time of data collection | 9.6±2.4 yr |
| Sex (male:female) | 25 (59.5):17 (40.5) |
| Seizure onset (classic) | 30 (69.8) |
| Typical semiology | 35 (81.4) |
| Developmental delay | 11 (25.6) |
| Initial treatment (ACTH) | 11 (25.6) |
| Treatment lag (<1 mo) | 28 (65.1) |
| Primary clinical responder | 18 (41.8) |
| Primary EEG responder | 18 (41.8) |
| Unfavorable outcome in follow-up | 22 (51.2) |
| Moderate | 8 (36.4) |
| Severe | 12 (54.5) |
| Death | 2 ( 9.1) |

Abbreviations : ACTH, adrenocorticotropic hormone; EEG, electroencephalogram

**Table 3.** Risk Factors for Unfavorable Outcomes of Children with Infantile Spasms

| Risk factor vs. Reference | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI |
| Sex (male vs. female) | 1.59 | (0.47, 5.38) | 1.86 | (0.28, 12.29) |
| Onset of seizure (classic vs. early & late) | 1.49 | (0.34, 5.74) | 1.55 | (0.17, 14.46) |
| Typical semiology (typical vs. atypical) | 1.33 | (0.26, 6.83) | 1.40 | (0.30, 6.70) |
| Developmental delay (present vs. absent) | 1.54 | (0.11, 11.83) | 1.65 | (0.19, 14.38) |
| Etiology (symptomatic vs. cryptogenic) | 2.09* | (0.55, 7.91) | 1.12 | (0.16, 7.91) |
| Treatment lag (<1 mo vs. ≥1 mo) | 0.61 | (0.17, 2.21) | 0.81 | (0.48, 1.36) |
| Initial treatment (ACTH vs. others) | 0.81 | (0.45, 1.34) | 0.82 | (0.45, 1.40) |
| Primary outcome† (non-response vs. response) | 25.14* | (1.46, 234.17) | 20.47* | (1.93, 160.98) |

*$P$ value less than 0.05
†cessation of seizure or EEG response after initial treatment
Abbreviations : OR, odds ratio; CI, confidence interval; ACTH, adrenocorticotropic hormone; EEG, electroencephalogram

children with drug-resistant epilepsy. In another study, 83 % of 10-year-old children with a history of IS had mental retardation (IQ≤70) and 56% had profound mental retardation (IQ≤20)[17]. Our results are consistent with these findings, in that 72.1% (n=31) of our children with IS had at least mild neurodevelopmental disorders or died and 46.5 % (n=20) had moderate to severe neurodevelopmental disorders. In addition, both patients who died suffered from severe physical restrictions before death.

Because of poor prognosis despite treatment, identification of risk factors predisposing to poor long-term outcomes, including neurodevelopment disorders and mortalities has been one of main issues[3-7]. Despite the inconsistent methodology in these studies, several factors have been identified, including symptomatic etiology, abnormal development at the time of diagnosis, long treatment lag (>1 month), poor response to initial treatment, and recurrent relapse. Above all, underlying pathology (symptomatic etiology) is the most important factor in determining patient outcomes[3-7]. For example, severe brain malformation, postinfectious etiology[18], and tuberous sclerosis[19] have been associated with more unfavorable prognosis. In contrast, patients with cryptogenic etiology, in which no causes can be identified, have a good prognosis. We found that 39.5% of children with symptomatic IS, but only 11.7% of those with cryptogenic IS, had unfavorable outcomes. In addition, none of the children with cryptogenic IS had a severe neurodevelopmental disorder.

Statistical analysis showed that the difference between the symptomatic and cryptogenic groups approached statistical significance at the univariate, but not at the multivariate level (Table 3). We surmise that successful neurosurgery for intractable epilepsy and vigabatrin for tuberous sclerosis, which are known to be particularly effective[20, 21], may have weakened the association between etiology and long-term outcome. Of the 5 children with symptomatic IS who underwent neurosurgery, 4 showed normal neurodevelopment or mild developmental disorders. Of the 72 children with IS, four had tuberous sclerosis and were treated with vigabatrin; of these, 1 developed normally and 3 were lost to follow-up, but 2 of these 3 children showed cessation of spasms after initial treatment.

Another prognostic factor is primary clinical and electroclinical outcomes[3-7]. A study in a large population found that 97.0% of patients with favorable long-term outcomes were electroclinical responders to initial treatment[3]. We found that non-response to primary treatment was significantly related to neurodevelopmental disorders with high OR in both univariate and multivariate analysis (Table 4). The prevalence of unfavorable outcomes in non-responders was two-fold higher than in responders. Furthermore, non-responders with symptomatic IS had the highest prevalence of unfavorable outcomes.

We found that the remaining risk factors, including developmental delay at time of diagnosis and treatment lag, were not related to neurodevelopmental outcomes. Children with pre-existing developmental delay or neurological deficits at time of diagnosis have been thought to be related to less favorable developmental outcomes[8]. This tendency may be related to the association between the underlying causes of IS and pre-existing developmental disorders. Children with symptomatic IS had a higher prevalence of pre-existing developmental delay. Although it is not clear if treatment lag is a risk factor, several reports have emphasized the importance of rapid treatment initiation[22, 23]. A study of 286 children with IS found that initiation of treatment within 30 days was significantly related to better long-term outcomes than initiation after 30 days[23].

In conclusion, despite this study suffers from a small patient population with a large percentage of patients lost to follow-up and weak validity of the questionnaires to predict long-term neurodevelopmental status, our findings indicate several important things determining long-term neurodevelopmental outcomes for children with IS. First, the majority (72.1%) of children with IS had unfavorable neurodevelopment. Second, children with symptomatic IS had significantly poorer outcomes in univariate analysis than those with cryptogenic IS. Third, new epilepsy treatment modalities, such as vigabatrin and neurosurgery, may have counteracted the poor outcomes in select patients with symptomatic IS, thought to weaken the association between etiology and long-term outcome in multivariate

**Table 4.** Unfavorable Long-term Outcome of Children with Infantile Spasms and Response to Initial Treatment (Primary Electroclincal Outcome) in Infancy

| | No. of subjects | |
|---|---|---|
| | Cryptogenic (n=13) (%) | Symptomatic (n=30) (%) |
| Primary responders | 6 (46.2) | 12 (40.0) |
| Unfavorable outcomes | 1 (16.7) | 4 (33.3) |
| Primary non-responders | 7 (53.8) | 18 (60.0) |
| Unfavorable outcomes | 4 (57.1) | 13 (72.2) |

analysis. Fourth, non-response to initial electroclinical treatment was significantly related to unfavorable long-term outcomes, indicating that the initial control of seizures may be important in reducing the occurrence of poor neurodevelopment.

## 한 글 요 약

### 영아 연축 환아의 장기적 예후에 관한 고찰

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**목 적**: 이 연구의 목적은 영아 연축 환아들의 장기적 예후를 분석하며 그들의 신경학적 발달지연에 영향을 주는 예후인자들을 찾고자 한다.

**방 법**: 저자들은 1994년에서 2007년까지 서울아산병원에서 영아 연축으로 진단받은 72명의 소아들에 대하여 후향적 분석을 시행하였다. 이들 중 43명에 대한 전화 상 질문서 및 의무기록을 통하여 현재의 신경학적 발달에 대한 평가를 시행하였다. 불량한 장기적 예후와 관련된 인자들의 확인을 위해 로지스틱 회귀분석을 사용하였다.

**결 과**: 13명(30.2%)이 특발성이며 30명(69.8%)이 증후성이었다. 11명(25.6%)이 ACTH 치료에 반응하였으며, 치료지연은 1.3±1.9개월이었다. 18명(41.8%)이 초기치료에 호전된 반응을 보였으며, 평균 추적기간은 7.2±1.5년이었다. 장기 예후 분석에서는 22명(51.2%)이 중등도 이상의 신경학적 발달지연을 보였으며, 그 중 2명(4.8%)이 사망하였다. 단변량 분석에서는 증후성 영아 연축과 초기 치료에 불량한 반응이 중등도 이상의 신경학적 발달지연과 관련된 유의한 위험인자였으나, 다변량 분석에서는 초기 치료에 불량한 반응만이 위험인자로 확인되었다.

**결 론**: 영아 연축 환아의 전반적인 예후는 불량하였고 초기치료에 불량한 반응을 보인 환자군에서 장기적 예후가 더욱 불량하였다. 이러한 결과는 경련의 초기 조절이 영아 연축 환아에서 신경학적 발달지연과 관련된 장기적 예후에 영향을 줄 수 있음을 시사한다.

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