Long-term Cognitive Outcomes of a Cohort of Children with Cryptogenic Infantile Spasms Treated with High-dose Adrenocorticotropic Hormone

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Summary: Purpose: To evaluate the outcome of children with cryptogenic infantile spasms treated with high-dose synthetic adrenocorticotropic hormone (ACTH) and the relation between early treatment, within 1 month of onset, and outcome.

Methods: We assessed the long-term cognitive and seizure outcomes of 37 patients with cryptogenic infantile spasms (onset, age 3 to 9 months) receiving standardized treatment regimen of high-dose tetracosactide depot, 1 mg IM every 48 h for 2 weeks, with a subsequent 8- to 10-week slow taper and followed by oral prednisone, 10 mg/day for a month, with a subsequent slow taper for 5 months or until the infant reached the age of 1 year, whichever came later. Development was assessed before treatment. Seizure outcomes were followed up prospectively. Cognitive outcomes were determined after 6 to 21 years and analyzed in relation to treatment lag and pretreatment regression.

Results: Twenty-two infants were treated within 1 month of onset of infantile spasms, and 15 after 1 to 6.5 months. Normal cognitive outcome was found in all 22 (100%) patients of the early-treatment group, and in 40% of the late-treatment group. Normal cognitive outcome was found in all 25 (100%) patients who had no or only mild mental deterioration at presentation, including four in the late-treatment group but in only three of the 12 patients who had had marked or severe deterioration before treatment.

Conclusions: Early treatment of cryptogenic infantile spasms with a high-dose ACTH protocol is associated with favorable long-term cognitive outcomes. Once major developmental regression lasts for a month or more, the prognosis for normal cognitive outcome is poor. Further studies are needed on the optimal treatment regimen for this disorder. Key Words: Cryptogenic infantile spasms—ACTH—Prognosis.
spasms was based on the descriptive clinical history of massive spasms including direct observation by the staff in some, or documentation by videotape, and the presence of hypsarrhythmic activity on the sleep EEG recording (1). The criteria for the diagnosis of cryptogenic infantile spasms were normal neurodevelopment before the onset of spasms, based on information obtained from the parents, the referring physician, and the medical chart of the well-baby clinic; normal findings on computed tomography of the brain; absence of other types of seizures before or concomitant with the onset of spasms; and no known etiology (1,4).

Inclusion criteria for the study were cryptogenic infantile spasms, symmetric hypsarrhythmia, absence of focal slowing or regional spike discharges on the EEG suggestive of focal brain dysfunction (1,4,17,18), and a standardized treatment protocol of high-dose synthetic ACTH from the start. Of the 156 patients referred for the treatment of infantile spasms, 111 were excluded because of they did not meet the criteria for cryptogenic infantile spasms. An additional eight children were excluded because they had been treated with initial low doses and/or short-duration ACTH therapy. The remaining 37 infants formed the study group.

Subjects all had EEGs performed at baseline and at 1, 2, 4, 8, and 10 weeks after initiation of ACTH therapy; 1, 3, and 5 months after institution of prednisone (i.e., before each dosage reduction); and 1 month after discontinuation of treatment. All EEGs were performed by using either 12- or 14-channel EEG machines, and each record was made for a minimum of 30 min. Thus each subject had ≥10 EEGs performed with a total duration of >5 h.

**Magnetic resonance imaging**

In our hospital, MRIs became available only in 1988, and the use was restricted, with long waiting periods. Thus MRI was not indicated by the criteria of the health service in the 22 subjects in the early-treatment group and for the five cases in the late-treatment group who are seizure free with normal cognitive outcome. Of the remaining 10 cases in the late-treatment group, seven were entered prior to 1988. MRIs were performed subsequently in case 10 at age 12, case 12 at age 10, case 14 at age 6, and case 15 at age 4, and were normal in all four. In cases 2 to 7, MRI was not done, as they were unable to cooperate, and it would have required general anesthesia.

**Early identification**

During a previous study (7), it became clear that the majority of infants with infantile spasms were being referred to our clinic late in the course of the disease, by which time developmental deterioration was pronounced. To increase awareness of the importance of early diagnosis and treatment of infantile spasms, we implemented in 1974 an educational program of lectures and written information on early diagnosis geared to primary physicians and public health nurses in the community. The mild initial clinical symptoms were stressed, as well as the characteristic features of the two main forms of spasms, which are not always identified by parents as abnormal; the flexor type, often dismissed by parents as “colic,” and the extensor type, often interpreted as a startle response or an expression of irritability. We further noted that parents sometimes complain of their infant’s irritability even without describing the spasms unless specifically questioned. After the implementation of this educational intervention, the majority of affected infants were being referred within 1 month of the onset of symptoms.

Parents were closely questioned about the time of onset of spasms to determine the delay in diagnosis and treatment. Patients treated within 1 month of onset of the spasms were categorized as the early-treatment group, and those treated after 1 month, as the late-treatment group. The study was approved by the ethics committee of Rabin Medical Center, Petah Tiqva, Israel.

**Initial evaluation**

At the time of presentation, all patients underwent neurologic examination and baseline laboratory studies before initiation of treatment that included complete blood count; serum electrolytes; calcium, phosphorus, glucose, and blood urea nitrogen levels; and urinalysis. Serum amino acids, lactic acid, pyruvic acid, urine amino acids, and organic acids were measured in some patients.

All infants underwent assessment of developmental deterioration before treatment, with emphasis on behavior and object manipulation, which are better correlated with intelligence than is gross motor development (19). Parents were questioned about regression in smiling, interest in the surroundings, eye tracking, alertness, response to sound, vocalization, and object manipulation. A detailed assessment of development was performed clinically. Duration of regression also was noted. Developmental deterioration was considered mild if there was decrease in smiling and/or alertness and interest in the surroundings; marked, if these signs were accompanied by decrease in eye contact, response to sound, vocalization, and object manipulation, with noticeable hypotonia; and severe, if the infant showed total lack of smiling and eye contact (complete visual inattention), lack of interest in the surroundings, drowsiness, and inability to manipulate objects.

**Treatment protocol**

The treatment protocol being used since April 1974 is as follows:

- **Stage 1**: Intramuscular tetracosactide depot (Synacthen) in decreasing doses for 10 to 12 weeks as follows: 1 mg every 48 h for 2 weeks; 1 mg every 72 h for 2 weeks; 1 mg once a week for 4 to 6 weeks; 0.5 mg once a week for 2 weeks.
- **Stage 2**: Oral prednisone in decreasing doses for ≥6 months or to the age of 1 year, whichever came later.
at the following doses: 10 mg daily for 1 month; 10 mg on alternate days for 2 months; 5 mg on alternate days for 2 months; 2.5 mg on alternate days for 1 month or until age 1 year, whichever is later. Prednisone was started within 24 h of the last dose of ACTH. Treatment was continued until age 1 year to avoid possible relapse during the high-risk period for infantile spasms.

Tetracosactide (Synacthen), which is a synthetic form closely related to ACTH, was used, as it avoided the need for daily injections, which at that time would have required daily trips to the hospital. Although the precise milligram depot-tetracosactide to International Units of ACTH relation is unclear, the best estimates are that 1 mg tetracosactide is equivalent to ~80 U to 100 U ACTH gel in terms of maximal plasma cortisol concentration (20–22). However, depot-tetracosactide has a longer duration of action; mean plasma level had returned to normal by 24 h after the corticotropin gel, and by 48 h after 1 mg depot-tetracosactide. Treadwell and Dennis reported (21) that with a dose of 1 mg tetracosactide, adrenal stimulation lasts 48 h, and plasma 11-OHCS levels may still be slightly increased even beyond this period, indicating that administration every 2 days may suffice.

EEGs were performed at baseline and at 1, 2, 4, 8, and 10 weeks after initiation of ACTH therapy, 1, 3, and 5 months after institution of prednisone (i.e., before each dosage reduction), and 1 month after discontinuation of treatment. If hypsarrhythmia persisted 2 weeks after institution of therapy, an additional EEG recording was made after the third week of treatment. In the event of a recurrence of spasms and/or hypsarrhythmia during the initial period of prednisone dosage reduction, the dose was increased to the previous effective dose for ≥2 weeks, and if the spasms still continue, tetracosactide was reinstituted. If recurrence was noted toward the end of prednisone reduction, tetracosactide was reinstituted.

Cognitive outcomes

Cognitive assessment was determined after 6 to 21 years (to include only patients aged 6 years and older). The children attending regular schools were interviewed and tested individually with the Hebrew version of the Wechsler Intelligence Scale for Children (WISC-R). These tests are normed for Israel and are those used for standard psychometric testing. Those who completed high school also were interviewed individually, and their national high school matriculation records were examined. Children who were attending special education schools and those who were considered uneducable were classified as impaired but were not given formal IQ testing. In Israel, at the time of this study, the special education setting in which these children were enrolled was limited to those with mental retardation (IQ <70).

Seizure outcomes

Seizure outcomes were prospectively assessed on an ongoing basis. Seizure types and epilepsy syndromes were classified in accordance with the International League Against Epilepsy (ILAE) classification of seizures and epilepsy syndromes (1,23).

Data analysis

Data were analyzed by using standard statistical methods (24). The descriptive statistics included the age at onset, the occurrence of developmental deterioration before treatment, and early (within 1 month of onset) versus late treatment. Means for continuous variables such as age at onset and mean treatment lags were compared by using Student’s t test. Other comparisons of categoric outcomes (presence or absence of subsequent seizures, presence or absence of subsequent cognitive impairment) were made by using χ² statistics. The sample size is too small to permit the analysis of the possible effects of age at onset or precise treatment dose adjusted for body size on outcome. All p values were computed by using two-tailed distributions. A p value <0.05 was considered statistically significant.

RESULTS

Population characteristics

The 37 subjects in the study cohort consisted of 21 male and 16 female patients, all products of a normal pregnancy and delivery. Age at onset of spasms ranged from 3 to 9 months, and the interval between onset of spasms and initiation of ACTH treatment (treatment lag) ranged from 1 day to 6.5 months. The characteristics of the 22 patients treated within 1 month of onset of spasms (range, 1 day to 1 month; early-treatment group) are shown in Table 1, and of the 15 patients treated after 1 month of spasm onset (range, >1 month to 6.5 months; late-treatment group), in Table 2. The mean age at onset was 5.4 months for the early-treatment group and 5.9 months for the late-treatment group (p = 0.29).

In the late-treatment group, the age at onset was 4 to 9 months (mean, 5.9 months), and all had normal prior development. The delay in starting therapy was due to lack of recognition of the significance of the movements by the parent, who therefore did not discuss them with the physician in seven cases (cases 1, 3, 7, 8, 9, 12, and 15), failure to diagnose these on the part of the general physician in five cases (cases 2, 3, 4, 5, and 6), and misdiagnosis by pediatricians and emergency room physicians in four cases (cases 10, 11, 13, and 14). The cases with the longest treatment lag were all from the years 1974 to 1978 from general practitioners at that time. Aside from delay in diagnosis, nothing in the early development or history of these children distinguished them from the early-treatment group.
TABLE 1. Early-treatment group: patient profiles

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at onset (mo)</th>
<th>Treatment lag (wk)</th>
<th>Pretreatment developmental regression</th>
<th>Duration of regression (wk)</th>
<th>Cessation of clinical spasms (d)</th>
<th>Time to resolution of hypsarrhythmia (wk)</th>
<th>Relapse of spasms</th>
<th>Subsequent epilepsy</th>
<th>Subsequent outcome/IQ follow-up</th>
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</table>

IQ given as full scale/verbal/performance.

Pretreatment developmental status

The pretreatment developmental status of the infants before institution of treatment and the time frame of the deterioration are summarized in Tables 1 and 2. In the early-treatment group, six (27%) infants were developmentally normal, 15 (68%) showed mild deterioration, and only one had evidence of marked deterioration, which was observed simultaneously with spasm onset 3 days before starting treatment. In contrast, in the late-treatment group, two (13%) infants were developmentally normal, two (13%) showed mild developmental deterioration, and 11 (73%) had evidence of marked or severe developmental deterioration ($\chi^2 = 19.7; p < 0.001$).

Initial response to ACTH therapy

Clinical cessation of the spasms was achieved in 34 (92%) patients within 3 to 10 days of starting ACTH treatment (Tables 1 and 2). In the early-treatment group, the spasms were permanently controlled in all cases, and clinical control was achieved within 3 days in 19 (86.3%) of the cases (Tables 1 and 2).

TABLE 2. Late-treatment group: patient profiles

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age at onset (mo)</th>
<th>Treatment lag (mo)</th>
<th>Pretreatment developmental regression</th>
<th>Duration of regression (mo)</th>
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<th>Time to resolution of hypsarrhythmia (wk)</th>
<th>Relapse of spasms</th>
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IQ given as full scale/verbal/performance.
patients. In the late-treatment group, clinical cessation of spasms was achieved within 3 days in only four (27%) patients, and within 10 days in 12 (80%). Three (20%) patients in the late-treatment group continued to have clinical spasms after 10 days of treatment. The differences in response to therapy were statistically significant ($\chi^2 = 14.2; p < 0.001$).

The EEG normalized within 1 to 2 weeks of starting ACTH in all 22 (100%) patients in the early-treatment group (in 77% within 1 week and in 22.7% during the second week), and within 1 to 4 weeks in 11 (80%) patients in the late-treatment group (in 20% within 1 week and in 60% after week 1 to week 4). In the three (20%) patients of the late-treatment group who did not have a clinical response, the EEG also did not normalize. The differences in EEG response also were statistically significant ($\chi^2 = 13.7; p = 0.001$).

**Relapse of infantile spasms**

Three patients relapsed. One patient (Table 1, no. 11) in the early-treatment group had reappearance of hypsarrhythmia on the EEG without the reappearance of clinical spasms in the fifth month of prednisone treatment (5 mg on alternate days). The protocol was reinstituted from the start, and the EEG normalized within 2 weeks without further recurrence. Two patients in the late-treatment group (Table 2, nos. 5 and 7) relapsed. In both, the clinical picture evolved to the Lennox–Gastaut syndrome.

**Adverse effects of treatment protocol**

In all children, cushingoid features developed, and most of them exhibited irritability early in the course of treatment. In >50%, hypertension developed, and hypokalemia also was frequent. Both were treated when indicated. In no case was it necessary to discontinue treatment because of hypertension or electrolyte imbalance. The common infectious diseases of this age group, gastroenteritis, otitis media, and upper respiratory infections, occurred in our treatment group, but in the absence of a control group, it is difficult to evaluate their relation to treatment. Parents were given instructions about keeping the children away from other children and to come to the emergency department for any fever. No life-threatening infectious disease occurred. One case of osteoporosis was presumed related to treatment in a child in the late-treatment group (Table 2, no. 7) who had required two courses of therapy because of relapse.

**Long-term seizure outcomes**

In the early-treatment group, one patient exhibited seizures and EEG pattern consistent with benign partial epilepsy of childhood with centrotemporal spikes (1) at age 9 years. Complete recovery occurred 2 years later. In the late-treatment group, in seven (47%) patients, subsequent epilepsy developed. Of the 10 children who demonstrated a complete response to ACTH therapy, in two (Table 2, nos. 6 and 10), subsequent seizures developed with a benign clinical course. In the three patients who had failed to respond to treatment (Table 2, nos. 3, 4, and 14), as well as the two cases who relapsed and then did not respond (Table 2, nos. 5 and 7), the seizures evolved into Lennox–Gastaut syndrome with slow spike–wave discharge and polyspike waves (1).

The five children in the late-treatment group in whom intractable seizures developed, associated with the Lennox–Gastaut syndrome (Table 2, nos. 3, 4, 5, 7, and 14), had marked (no. 7) or severe (nos. 3, 4, 5, and 14) developmental regression of ≥1.5 months duration before onset of treatment. Even within the late-treatment group, the mean treatment lag before therapy in this group (3.9 months) was higher than that in the other 10 children with more-favorable seizure outcomes (mean, 2.3 months; $p = 0.079$).

**Long-term cognitive outcomes**

Cognitive outcomes for the subjects are shown in Tables 1 and 2. In the early-treatment group, all 22 subjects had normal cognitive outcomes as evidenced either by verbal, performance, and full scale IQs >100 (n = 12), completion of high school matriculation examination (n = 7), or attendance in a normal school setting without difficulties (n = 1). In the late-treatment group, only six (40%) of subjects were of normal intelligence, as evidenced by normal IQs (n = 4), completion of matriculation examination (n = 1), or functioning well in a regular classroom (n = 1). One subject was of borderline intelligence, and the remaining eight had mental retardation, which was moderate to severe in five. The differences were highly significant ($\chi^2 = 17.4; p < 0.001$). If one limits the analysis of the late responders to the 10 patients who responded to the initial ACTH therapy without relapse, then one finds that six had a normal cognitive outcome, one child (Table 2, no. 15) was of borderline intelligence, and three had mental retardation. Even limiting the comparison of cognitive outcomes to those who responded to initial therapy without relapse of the infantile spasms, the differences between the early-treatment and late-treatment groups are still highly significant ($p < 0.001$). Even within the late-treatment group (Table 2), the mean treatment lag in the six children with normal developmental outcomes was 1.9 months compared with 3.5 months in those with poor developmental outcomes ($p = 0.014$).

The degree and duration of developmental decline before treatment also was significantly associated with outcome. In the overall group, all 25 children who were developmentally normal (n = 8) or had evidence only of mild developmental regression (n = 17) before onset of treatment had normal cognitive outcomes compared with only three (25%) of 12 children with evidence of marked or severe regression before onset of treatment ($p < 0.001$). Among the 12 children with evidence of
marked to severe regression, the three children (one in early-treatment group and two in late-treatment group) in whom the duration of the deterioration before onset of treatment was \( \leq 1 \) week all had normal cognitive outcomes compared with none of the nine children with marked to severe developmental regression, in whom the duration of the regression before initiation of treatment was 1 to 4 months \( (\chi^2 = 10.1; p < 0.002) \).

In the present study, many children had measured IQs > 100; whether this reflects the primarily middle class population being studied or some other explanation is unclear. What is clear is that they at the very least have a normal IQ, which is the important outcome for this study.

**DISCUSSION**

**Cognitive outcome in infantile spasms**

Mental retardation is a common and serious sequel of infantile spasms that has been reported in 71% to 88% of patients (2,3,8,25). However, in most treatment trials, the proportion of symptomatic cases is between 85% and 91% (3,6,8,11). As cognitive outcome in these cases is influenced by the underlying preexisting pathology, it is difficult to draw conclusions about the efficacy of treatment on cognitive outcomes in these cases (2,4). Unfortunately, the number of cryptogenic cases in most series is far too small to permit meaningful comparison of cognitive outcomes. Interestingly, in one recent population-based study from Iceland, the cases of cryptogenic infantile spasms were all seizure free and developmentally normal (26).

**Cognitive outcome and treatment**

Two prospective studies evaluated long-term cognitive outcomes in children with cryptogenic infantile spasms (6,9). Glaze et al. (6), by using low-dose ACTH (20 to 30 U/day) or prednisone (2 mg/kg/day) for 2 to 6 weeks, reported that of the eight cryptogenic cases, only three (38%) were normal or mildly mentally impaired at follow-up. In this small-scale study, no differences in outcome were found between the five patients treated early (within 5 weeks of spasm onset) and those treated later. In contrast, the much larger, prospective study of Lombroso (9), which included 90 children treated with hormone therapy and followed up for 6 years, reported that approximately half the children treated early with high-dose ACTH (110 U/m²/day) had normal cognitive outcomes. In this nonrandomized study, a higher proportion of those treated with high-dose ACTH had favorable cognitive outcomes than did those treated with prednisone, 2 mg/kg/d (50% and 12%). Furthermore, the proportion with normal cognitive outcomes in the ACTH-treated group was higher in those treated early than on those treated late (52% vs. 27%).

This finding of the importance of early treatment also is supported by numerous retrospective studies (3,5,7,8,10,27,28). Singer et al. (28), with high-dose, long-duration ACTH therapy, reported that eight of nine children with cryptogenic infantile spasms treated within 1 month of spasm onset achieved normal development, whereas none of the 10 treated later had a normal developmental outcome.

**Effect of developmental regression on outcome**

Cognitive dysfunction during the acute stage of hypsarrhythmic EEG discharges has been reported (29,30). It also is well established that prolonged hypsarrhythmia may lead to subsequent cognitive impairment (6,8,27,28). Therefore to evaluate the effect of treatment on long-term cognitive outcome, the degree and duration of developmental deterioration before onset of treatment must be considered. Furthermore, the major impact of early treatment may be to prevent irreversible cognitive decline. Despite the evidence that hypsarrhythmia in the active stage leads to developmental deterioration, whose severity is strongly correlated with its duration, some patients may have a milder natural course or even spontaneous remission, as reported by Bachman (31). Because we cannot predict the clinical course, aggressive early treatment remains the most appropriate course.

**Strengths and weaknesses of these data**

The strength of this cohort is that it is a large longitudinal series of children with cryptogenic infantile spasms, uniformly treated, and with excellent long-term follow-up and formal cognitive assessments by an experienced group of epileptologists. Several weaknesses occur in this data set. The group was not randomized to different treatments, which precludes definitive statement about the optimal therapeutic regimen. The lack of randomization also makes it possible that undetected biases existed, which made the two groups have different underlying features that may have influenced outcome. The group was assembled before the widespread availability of MRI, and therefore the imaging modality used was computed tomography, which is inferior to MRI in detecting cortical dysplasia and other malformations (32). Whereas most cases of infantile spasms with focal MRI abnormalities have focal EEG findings (4) and these were excluded from the study, and the four MRIs performed in the delayed treatment were all normal, it is possible that the delayed-treatment group was biased toward symptomatic cases and that this accounts for some of the differences. Of particular concern would be the six children with poor neurologic outcomes in the delayed-treatment group who could not be imaged because of lack of ability to cooperate. Even within the delayed-treatment group, however, outcome was more a function of whether significant regression had already taken place than of delay per se.

Another weakness in the study is the lack of video-EEG confirmation of efficacy. This is the current standard, but was not widely used at the time this cohort was assembled. It is unlikely to be a major issue for several reasons. The clinical criterion used was complete cessation of spasms.
Although the rate of reported spasms by observers often seriously underestimates the true frequency, a much better correlation occurs with reported complete cessation. Second, all the patients had serial sleep EEGs, which, although not as accurate as prolonged video-EEG, are reasonable in this clinical setting. Finally and most important, no claims are being made comparing this treatment protocol with more recent randomized trials regarding short-term efficacy. Rather we are examining the relation of early aggressive therapy to long-term cognitive outcomes.

**Specific treatment protocol**

What is the optimal treatment protocol for infantile spasms? Class I double-blind randomized studies demonstrated that both ACTH and vigabatrin are effective in treating infantile spasms (14,15,33). In addition, a randomized double-blind class I study by Baram et al. (14) demonstrated that “high” dose ACTH is superior in efficacy to prednisone. The end point in all these studies was elimination of both clinical infantile spasms and hypsarrhythmia, as documented by video-EEG. However, none of these studies addressed the long-term cognitive outcomes of the children, nor were they capable of doing so. This limitation stems both from the short-term duration of follow-up in these randomized trials and from the lack of power to detect such difference, as the vast majority of infants had symptomatic infantile spasms, and very few cryptogenic patients were in each treatment arm. Therefore only the observational studies are available now. As the ultimate goal of treating infantile spasms is improved cognitive as well as seizure outcomes, future treatment protocols must try to address long-term as well as short-term outcomes to define the optimal therapeutic approach. The present results suggest that favorable long-term outcomes are a realistic goal when it comes to cryptogenic infantile spasms.

**Duration of therapy**

Clinical spasms and the hypsarrhythmic EEG abnormalities often resolve on treatment within a few days, with cessation of seizures and disappearance of the hypsarrhythmia (7,14,15). Many studies have therefore used a short course of therapy. This has the obvious benefit of minimizing the potential morbidity of therapy. Our purpose in prolonging therapy was to prevent relapse. Earlier studies have reported relapse rates of one third or higher (4,34), whereas in the present study, relapse occurred in only three (8%) patients. Both in our study and in others, children whose infantile spasms relapse are unlikely to have a subsequent sustained response to steroid therapy (4). The side effects of treatment in our cohort were relatively mild, given the severity of the illness being treated.

As no control arm exists of either low dose or short duration of therapy, no firm conclusions can be drawn about the optimal treatment protocol for cryptogenic infantile spasms. However, our own experience in the 1960s showed poor results in patients treated with low-dose ACTH or corticosteroids (7). In the prior study, in the early-treatment group, normal cognitive outcomes were more likely to occur in those treated with high-dose ACTH compared with those given low-dose ACTH (7).

**CONCLUSION**

In conclusion, the long-term prognosis of cryptogenic infantile spasms is good to excellent in nearly all of the affected children with a prolonged treatment protocol that extends to age 1 year or older, provided that the treatment is started within a month after the onset of spasms. The results suggest that the outcome is significantly poorer in those children whose ACTH therapy is delayed beyond 1 month after spasm onset, particularly if evidence of developmental regression is present. The data about the poorer outcome in the late-treatment group must be interpreted with caution, as the groups were not randomized to early and late therapy and because of the possibility that children with hidden symptomatic etiology were present in the late-treatment group. Further research is needed on defining the optimal treatment regimen in terms of the precise dose and duration of therapy needed. Early treatment depends on early diagnosis, which unfortunately is often delayed because symptoms are so likely to be mis-interpreted (35).

**REFERENCES**


