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Original Article

# Outcome of synthetic adrenocorticotropin hormone treatment in children with infantile spasm

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## Abstract

***Background*** Infantile spasms (IS) is an age-specific epilepsy syndrome characterized by flexor, extensor, and mixed flexor-extensor spasms which often occur in clusters during the first 2 years of life. IS is often difficult to manage with the usual anti-epilepsy drugs (AEDs). Therapy with adrenocorticotropin hormone (ACTH) has been used since 1958. In Indonesia, ACTH usage is still rare.

***Objective*** This study aims to examine the effectiveness of ACTH as an anti-epileptic drug in managing IS.

***Methods*** This was descriptive retrospective cohort study. Subjects were IS patients who visited the neurology outpatient clinic in Sanglah Hospital, Bali, from January 2007 until June 2010. Each subject received AED(s) plus either ACTH or methylprednisolone for 4-6 weeks.

***Results*** There were 19 IS patients over the four year duration of this study. They were mostly boys (11), aged 2 weeks to 17 months, with a mean age at treatment of 9 months. Eighteen patients received polytherapy, while one patient received only phenobarbital as monotherapy. Most patients who received ACTH (13/16) had a seizure-free period, while the 3 that did not receive ACTH continued having seizures. Patients who received ACTH showed a good response (seizure-free) after 5-13 days therapy and their EEG pattern showed disappearance of burst suppression within 1-2 weeks. ACTH side effects included weight gain and cushingoid appearance. One patient died from pneumonia.

***Conclusions*** Diagnosis of IS should be considered in patients presenting with spasms at less than 6 months old. IS treatment should begin as soon as possible. IS patients responded well to a short course of ACTH therapy. **[Paediatr Indones. 2011;51:94-100]**.

***Keywords***: *Infantile spasms, hypsarrhythmia, ACTH*

Infantile spasms (IS) is an age-specific epilepsy syndrome characterized by flexor, extensor, or mixed flexor-extensor spasms which often occur in clusters during first 2 years of life. West syndrome is diagnosed when IS, hypsarrhythmia, and mental retardation are present, though diagnosis can be made even if one of the three elements is missing.[1] IS are characterized by uncontrolled seizures and associated with severe mental retardation. In some cases, severe mental retardation is caused by underlying diseases, such as lichencephaly or porencephaly. Early diagnosis and treatment to control seizures is important so that a better developmental outcome can be achieved.[2] The incidence of IS is estimated to be 0.25 - 0.60 per 1000 live births, and the prevalence is 0.15 - 0.2 per 1000 children aged 10 years or younger.[3,4] Several studies have reported similar ages of onset for IS, with 90% occurring before 1 year of age and a peak onset at 4-6 months.[5] IS can be divided into three types: flexor, extensor, and mixed flexor-extensor spasms.[5,6] IS prognosis is poor despite treatment. However, if treatment is started within 1 month of symptom

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onset, better seizure control and development may be observed.[7,8]

IS etiology can be divided into symptomatic, cryptogenic, and idiopathic types.[9,10] Hypsarrhythmia is typically seen in the interictal EEG of IS patients, but not in all. In fact, hypsarrhythmia is not specific for IS because it also can be found in other epilepsy syndromes.[11-13] IS is difficult to treat with normal AEDs, as shown in more than 50 research studies.[14,15] Hormonal therapy with ACTH has been used since 1958 and in an American survey, 88% of respondents used ACTH for any type of IS.[16] In the United Kingdom, the initial treatment choice was influenced by etiology, and vigabatrin was the most frequently used first-line agent.[17-19] Hormonal therapy with synthetic ACTH (tetracosactrin) is well known in Indonesia, but the use of this drug is rare due to its limited availability. In the Department of Child Health, Udayana University Medical School, Sanglah Hospital, Denpasar, Bali, multiple AEDs are used to treat IS. The aim of this study was to examine the clinical progression and effectiveness in the use of multiple AEDs, including synthetic ACTH, regardless of IS etiology.

## Methods

We conducted this retrospective cohort study of IS patients who visited the pediatric neurology outpatient clinic from January 2007 to June 2010. The ethics committee of Sanglah Hospital, Denpasar, Bali approved the study. Data was collected consecutively and diagnoses were established by history taking, observance of clinical manifestations, and electroencephalography (EEG). Subjects' gender, age at diagnosis, age at onset of seizure/spasms, neonatal seizure history, underlying etiology, type of spasms, classification, developmental status, neurological deficits, EEG features, and neuroimaging (head CT scan) were obtained. Therapy was based on treatment protocols for IS**,** with a minimum six months follow-up. After IS diagnosis, monotherapy with an AED was begun. Patients whose parents agreed were given ACTH for 4-6 weeks, then continued with other AED as monotherapy or polytherapy. Those whose parents refused ACTH were given monotherapy non-ACTH AED, along with methylprednisolone. At subsequent follow-up checks, if seizures were not controlled patients were given a second monotherapy AED course, and if seizures continued uncontrolled then polytherapy AEDs were given.

## Results

From January 2007 until June 2010, there were 19 IS patients from the Pediatric Neurology outpatient clinic in Sanglah Hospital, Denpasar Bali. From the 19 patients, 11 were boys. Patients' ages during time of diagnosis and initial therapy ranged from 2 weeks-17 months, with the highest incidence at age > 12 months (6 cases). History of neonatal seizures was found in 5 cases. Most subjects had good nutritional status, but 4 suffered from severe malnutrition. Based on the underlying etiology, prenatal factors was the most common (11/19). Of the IS types, flexor type was found in 12, mixed flexor-extensor type in 6, and extensor type in 1. Age of seizure onset mostly occurred at 3-6 months of age (11/19). (**Table 1**) There were significant time lags between the age of onset of spasms and the age of IS diagnosis and treatment.

Most patients (16/19) were symptomatic type; one patient was idiopathic, and two patients were classified as cryptogenic because of incomplete data (limited supporting examination), so their etiology could not be determined. In the symptomatic group, prenatal etiologic factors (brain abnormalities, hydrocephalus, white matter disease, prematurity, congenital infection) were found in 11 patients, perinatal factors (HIE) in 4 patients and post-natal factor (neonatal meningitis) in 1 patient. The idiopathic subject had controlled seizures (with valproic acid + ACTH) along with normal development. Head CT scan was performed on all subjects revealing the following conditions: brain atrophy (10/19), lichencephaly (1/19), hydrancephaly (1/19), porencephaly (1/19), hydrocephalus (1/19), intracranial calcification (1/19), white matter disease (1/19) while 3/19 were within normal limits. Based on EEG examination, hypsarrhythmia was seen in only 5 patients, with the remainder having hypsarrhythmia modified by burst suppression (12/19) and severe hypofunction with multifocal epileptiform waves (2/19).

AED therapy may be in the form of monotherapy or polytherapy. Synthetic ACTH (tetracosactrin) was

**Table 1**. Characteristics of 19 patients with IS.

| Characteristics | Total (n) |
|---|---|
| Sex | |
| Boys | 11 |
| Girls | 8 |
| History of neonatal seizures | |
| Yes | 5 |
| No | 14 |
| Age at diagnosis and initial treatment, months | |
| 0 - < 3 | 3 |
| 3 - < 6 | 3 |
| 6 - <9 | 4 |
| 9 - 12 | 3 |
| >12 | 6 |
| Age of spasm onset, months | |
| 0 - < 3 | 6 |
| 3 - < 6 | 11 |
| 6 - 9 | 2 |
| Underlying etiology | |
| Prenatal | 11 |
| Perinatal | 4 |
| Postnatal | 3 |
| Other (uncertain classification) | 1 |
| Nutritional status | |
| good | 6 |
| mild/moderate malnutrition | 5 |
| severe malnutrition | 4 |
| overweight | 4 |
| Type of Spasms | |
| Flexor | 12 |
| Extensor | 1 |
| Mixed flexor-extensor | 6 |

**Table 2.** Seizure response to AED therapy.

| Therapy | Controlled Seizures | Uncontrolled Seizures | n |
|---|---|---|---|
| 1 AED | 0 | 1 | 1 |
| 2 AEDs | 5 | 3 | 8 |
| 3 AEDs | 7 | 1 | 8 |
| 4 AEDs | 1 | 1 | 2 |
| Total | 13 | 6 | 19 |

used at Sanglah Hospital beginning October 2008, but it was not always available. As an initial therapy, most patients (16/19) received synthetic ACTH. Other AEDs used were phenobarbital, valproic acid, methylprednisolone, clonazepam, clobazam, topiramate, and levetiracetam. Clinical response to AED therapy is shown in **Table 2**.

Of the 13/19 patients with controlled seizures, all patients received polytherapy with 2-4 AEDs, including ACTH. Of the 6 /19 patients with uncontrolled seizures, 3 patients received ACTH and 3 did not, due to lack of ACTH availability or lack of parental consent. The majority of patients receiving ACTH

**Table 3.** Seizure response to ACTH.

| ACTH therapy | Controlled Seizures | Uncontrolled Seizures | n |
|---|---|---|---|
| ACTH | 13 | 3 | 16 |
| No ACTH | 0 | 3 | 3 |
| Total | 13 | 6 | 19 |

**Table 4.** Seizure response to AED therapy based on IS classification.

| Classification | Controlled Seizures | Uncontrolled Seizures | n |
|---|---|---|---|
| Idiopathic | 1 | 0 | 1 |
| Symptomatic | 11 | 5 | 16 |
| Cryptogenic | 1 | 1 | 2 |
| Total | 13 | 6 | 19 |

(13/16) were free of seizures. In contrast, seizures in the 3 patients not taking ACTH were completely uncontrolled. (**Table 3**) Response to ACTH appeared 5-13 days after therapy began, with the disappearance of clinical symptoms. Burst suppression features and/or hypsarrhythmia disappeared in 1-2 weeks.

The ACTH preparation available was synthetic ACTH containing tetracosactrin 1 mg/ml equivalent to 80 IU/ml. Initial dose of ACTH was 0.25 ml given once daily intramuscularly, and increased gradually every 3 days depending on the response. The maximal dose was 2 x 0.5 ml daily per patient. ACTH was given for 4-6 weeks and then tapered off for 2 weeks. Reported side effects were excessive weight gain and cushingoid appearance, which were reversible when the ACTH was stopped.

In patients with uncontrolled seizures, 5 were symptomatic and 1 was cryptogenic. Most patients with controlled seizures (11/13) were categorized as symptomatic as shown in **Table 4**. Patients with uncontrolled seizures became intractable and their epilepsy difficult to treat. Developmental abnormalities were observed in 18 patients. Cerebral palsy was found in as many as 7 patients, all classified as symptomatic. Patients' neurological status is shown in **Table 5**.

## Discussion

In our study, we had more males than females, similar to a UK study in 150 hospitals where 96 of

162 IS cases were male.[16] However, studies at Cipto Mangunkusumo, Jakarta in 1985-1995 and 2000-2005 reported IS to occur more frequently in females.[9,20] Age of IS onset ranged from 3 weeks to 11 months. Around 90% of cases started prior to 1 year of age. Past studies have reported the highest occurrence at the age of 4-6 months and 3-7 months.[4,15,21] Our study showed peak onset to occur at 3-6 months of age. Most patients' age at diagnosis and start of therapy was > 12 months, indicating a long time span between onset of disease and beginning of treatment. IS is difficult to diagnose in early stages, despite parents' reporting strange movements in their baby. It has been reported that shorter times between onset and ACTH treatment correlate with more favorable outcomes.[8] Children with IS have better seizure control and development if the treatment is started within 1 month of onset of symptoms.[22,23] Other studies have also concluded that treatment lag may be a prognostic factor.[5,24,25]

**Table 5.** Neurological status in 19 patients with IS.

| Neurological status | Classification | | | n |
|---|---|---|---|---|
| | Idiopathic | Symptomatic | Cryptogenic | |
| Normal | 1 | 0 | 0 | 1 |
| Cerebral palsy | 0 | 7 | 0 | 7 |
| Delayed development | 0 | 9 | 2 | 11 |
| Total | 1 | 16 | 2 | 19 |

In our study 18/19 patients had abnormal development. Studies at Cipto Mangunkusuma Hospital also reported abnormal development in IS patients: 49/53 in a 1985-1995 study and 34/36 in a 2000-2005 study.[9,20] After receiving treatment and undergoing a period free of seizures, 4/13 cases experienced significant improvement in developmental status. Of the cases showing improvement, one was classified as idiopathic, 1 as cryptogenic and 2 as symptomatic, while the remainder required further time to follow-up.

Based on etiology, IS may be classified as symptomatic, cryptogenic, and idiopathic. Most IS cases are classified as symptomatic,[26] as in our study with 16 symptomatic, 2 cryptogenic, and 1 idiopathic. The symptomatic percentage may be larger when supporting examinations such as MRI, PET scan, metabolic and genetic disorders tests are conducted.[16,27] CT-scan of the head was performed on all patients, with some showing brain developmental disruption (16/19) and other within normal limits (3/19). One patient categorized as idiopathic showed normal and responsive development to the administration of AED.

IS diagnosis was made based upon history taking and clinical manifestations, supported by EEG features.[1,5] In this study 12 subjects had EEG features of burst-suppression with or without multifocal epileptiform discharges, whereas hypsarrhythmia was found in 5 patients. The hypsarrhythmia feature, in particular, appears on interictal EEG examination when children are awake and in early phases of IS disease.[11,15] In our study, modified hypsarrhythmia EEG features were probably due to recording while the children were asleep, since most EEG recordings were done during sedation with chloral hydrate. Hypsarrhythmia may also not appear if IS disease is in a late phase.

Management of IS patients at the Department of Child Health, Udayana University Medical School, Sanglah Hospital, Denpasar Bali for the period of the study consisted of combinations of phenobarbital, valproic acid, prednisone, methylprednisolone, pyridoxine, clonazepam, clobazam, topiramate, and levetiracetam. Synthetic ACTH (tetracosactrin) was used since October 2008 when available. Typical first line therapy for IS are ACTH, vigabatrin, prednisone/methylprednisolone, nitrazepam (randomized controlled reports), pyridoxine, valproic acid, and zonisamide (open-label study reports). Second line therapy drugs include valproic acid (randomized controlled reports), felbamate, lamotrigine and topiramate (randomized controlled reports ).[17-19,28]

Hormonal therapy has been widely used in North America for over 50 years. ACTH treatment was first reported in 1958 to have a quick and dramatic

effect on spasms. Although there is controversy on ACTH use with regards to its efficacy, optimal dosage, length of administration, and predictive factor,[1,5] the American Academy of Neurology and the Child Neurology Society issued a recommendation that ACTH may be effective for short periods of IS therapy and hypsarrhythmia restoration (class I-II, level B), but there is not enough evidence to recommend the optimal dosage and period of ACTH therapy (level U). Oral corticosteroids did not prove to be effective for IS therapy (level U). Vigabatrin may also be effective for short periods of IS therapy (class III-IV, level C), though retinal toxicity should be closely observed as a side effect, and there is little data to recommend frequency and screening test methods to reduce complications in children (class IV, level U). In addition, there is not enough evidence to recommend valproic acid, benzodiazepine, pyridoxine, zonisamide, topiramate, IVIG, liposteroid, as well as ketogenic diets and thyrotropin-releasing hormone (THR) for IS therapy (class III-IV, level U).[11,23] ACTH is used more selectively in European countries compared to prednisolone, whereas about 88% of senior pediatric neurologists in United States use ACTH as the first choice for initial therapy. The most frequently used regimen was a dosage of 40 IU/day for 1 to 2 months, and ACTH use was not influenced by etiology.[1,5] In a Japanese survey, treatment was influenced by etiology, and the order of drug selection was pyridoxine, valproic acid, and then synthetic ACTH at much lower doses than used in the United States. In a smaller survey of pediatric neurologists in the United Kingdom, the initial choice was influenced by etiology, and vigabatrin was the most frequently used first-line agent.[1,10] In our study, following the American Academy of Neurology recommendation, synthetic ACTH was given in alternating doses of 0.5 mg (40 IU)/ day for 4-6 weeks, then tapered off over 2 weeks. The mechanism of ACTH action may reduce neuronal excitability in IS by two mechanisms: inducing steroid release and direct, steroid-independent action on the melanocortin receptor. Additionally, suppression of corticotrophin-releasing hormone (CRH), an excitant neuropeptide, by ACTH/steroids was proposed as another mechanism for ACTH treatment of IS.[5] Natural ACTH has a duration of action of 12-18 hours, while its synthetic derivate, Zn tetracosactrin has a duration of action of 24-48 hours. A hundred units (100 IU) of natural ACTH is equivalent to 1 mg of tetracosactrin. ACTH dosages used are quite varied. A Japanese study used 3-14 IU/day dose and a Finnish study used 18-36 IU/day. Several reports recommend a day interval/alternating dose of tetracosactrin because its duration of action is longer.[1,13]

We observed that ACTH was effective for a short period of IS therapy. The preparation of ACTH is very important for IS therapy. In this study, ACTH was given with alternating doses of 0.5 mg/day IM, with 16/19 patients receiving ACTH, and 13/16 cases (81.3%) showed seizure-free status after 5-13 days and resolved EEG pattern after 1 – 2 weeks. Reported side effects of ACTH are hypertension, irritability, hyperglycemia, electrolyte disturbances, infections, weight gain, cerebral atrophy, and cushingoid appearance.[8,19] We observed weight gain and cushingoid appearance as ACTH side effects, as well as 4 cases of pneumonia, one of whom died.

Vigabatrin was recommended by several researchers for IS with symptomatic etiology, especially tuberosclerosis. Dosage was started at 20-30 mg/kg/day, with gradual increase until a clinical response was observed and EEG features restored. Maximum dose may be administered up to 100-200 mg/kg/day, but side effects of retinal toxicity and visual field impairment should be considered.[17,23] In this study, vigabatrin was not used because it was unavailable.

IS symptoms disappear spontaneously with or without therapy in most patients during the middle childhood period.[23] Other forms of convulsions (50%-70%) or intractable epilepsy (50%) will appear in patients with an IS history.[10,18] We cannot yet report the long-term outcome of patients due to limited follow-up time.

IS prognosis is poor despite treatment.[8,10,23] So far, the main factor in predicting prognosis for short term developmental status and epilepsy is IS etiology. Mental retardation has been reported in only 30%-50% of patients with cryptogenic etiology, but found in 80%-95% of symptomatic IS patients.[23,24] Prognosis is favorable when there is a normal neurological examination and developmental history at disease onset, along with short spasms and early ACTH therapy. Children with IS tend to have better seizure control and development if treatment is started within 1 month of symptom onset.[8] Most of our patients (18/19) started medication after three

months of symptoms, which likely resulted in less favorable prognoses.

We observed that all patients with symptomatic etiology (16/16) had a neurologic deficit. In this group, 7/16 suffered from cerebral palsy, in agreement with past studies. All patients from the cryptogenic group (2/2) also had neurologic deficits/ developmental delay, in contrast to past studies. It is possible that these 2 subjects would be included in the symptomatic group if further supporting examinations were conducted. The limitations of our study were: (1) head MRI and genetic/metabolic examination were not performed in all patients due to limitation of the facilities, resulting in 2 IS patients classified as cryptogenic since etiology could not be proven, and (2) longer term outcomes of patients could not be reported since more time was required for follow-up. Longer term patient outcomes may be a subject of subsequent studies.

We conclude that IS must be considered when a patient aged less than 6 months has spasms. IS must be diagnosed immediately and treated as soon as possible. We found that a short course of ACTH gave a better response than the other AEDs. While IS diagnosis is not difficult, its management in Indonesia may be challenging due to limited availability of ACTH. IS classification based on etiology is an important factor for prognosis with regards to therapeutic response and subsequent developmental status.

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