SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
THIRUVANANTHAPURAM - 695 011

PROJECT REPORT

NAME : **DR. SUJATHA P.**

PROGRAMME : **D.M. NEUROLOGY**

MONTH & YEAR OF SUBMISSION : **NOVEMBER 1999**

CERTIFICATE

I, **Dr.Sujatha P.** hereby declare that I have actually performed all the procedures listed / carried out the project under report.

Sujatha P

Signature

Place : Trivandrum

Date : 25.10.1999

Name in capital letters

SUJATHA P.

Forwarded, She has carried out the project under report.

Signature

Head of the Department

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCINES AND TECHNOLOGY TRIVANDRUM 695 011	Name	
	Page	of
	Date	

PROJECT REPORT

TITLE

INFANTILE SPASMS

- STUDY OF OUTCOME AND PROGNOSTIC FACTORS

NAME : DR. SUJATHA .P.

PROGRAMME : D.M. NEUROLOGY

MONTH & YEAR

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ACKNOWLEDGEMENT

My teacher Dr. K. Radhakrishnan, Professor and Head, Department of Neurology, has been my guide and mentor throughout my studentship in Neurology. I wish to express my heartfelt gratitude towards him for his constant guidance, supervision and encouragement.

I am also grateful to Mr. Sankara Sharma for his invaluable help in the statistical analysis.

I would also like to thank Miss. P. Rekha Moorthy for her secretarial assistance.

I am indebted to all the children and their parents for participation in this study.

SUJATHA. P.

CONTENTS

INTRODUCTION

Among the most frustrating tasks of the pediatric neurologist is the care of the child with infantile spasms. The disorder does not respond well to most therapeutic agents, and control of seizures does not necessarily lead to an improvement in developmental outcome[1].

On January 26, 1841, Dr.W.J.West of Tunbridge, England, wrote a letter to The Lancet in which he described the condition of his own son, a then 1-year old child[2]. He wrote about how his child, who was normal till 4 months of age, developed episodic bobbing forward of the head. 'This increased in frequency, and at length became so powerful as to cause a complete heaving of the head forward towards the knees .....'. This vivid account still remains one of the best possible clinical descriptions of infantile spasms Dr. West had rightly recognised that this disorder was age dependent, and peculiar to young infants.

With the availability of EEG, started the confusion in correct taxonomic placement of this disorder. In 1952, Gibbs and Gibbs defined the characteristic EEG pattern of infantile spasms viz. hypsarrhythmia, and propounded the concept of an original syndrome with specific clinical and EEG features[3]. The 1970 International Classification of Epileptic seizures placed infantile spasms in the category of generalised seizures with specific EEG characteristics[4]. This came under criticism because focal ictal features and focal brain lesions were not uncommon in children with infantile spasms. Moreover, the natural evolution of infantile spasms did not fall within the category of generalized epilepsiy[5]. These

difficulties were discussed at the workshop on infantile spasms, held at Abbaye de Royaumont, France in 19991, by the Commission on Pediatric Epilepsy of the ILAE [6]. They proposed that spasms should be listed as a special type of epileptic seizure in the International Classification of Seizures (commission 1981), and not be confined to the International Classification of Epileptic Syndromes (Commission 1989).

The reason underlying the above difficulty at correct taxonomic classification is the heterogeneity of the syndrome, inspite of relatively homogenous clinical manifestation. Investigations into its aetiology first began in the 1950s. In 1964, Jeavons and Bower described an idiopathic group, composed of cryptogenic and "doubtful" cases, and a symptomatic group with identifiable aetiology[7]. During the last 15 years, newer investigational modalities such as computerised tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) have revealed more information concerning the aetiopathology of infantile spasms. More and more of the 'cryptogenic group' of the past turns out to be symptomatic, in the light of above investigations.

Infantile spasms or West syndrome is a model for the study of epilepsy, because although the aetiology, clinical and EEG expression, and outcome vary greatly from one patient to another, there is now growing evidence that the underlying aetiology is the major determinant of both expression and outcome in a given patient[8]. This is why, therapy of the seizure per se may not alter

the outcome as expected, when the underlying aetiological factor is still operational. The increasing detection of focal brain abnormality by CT, MRI or functional brain imaging has influenced our understanding of the pathophysiology of infantile spasm. From the initial theory implicating brainstem as the unique source of clincal spasm and EEG hypsarrhythmia [9], there has been active research into the influence of focal cortical lesions. Chugani et al used PET to assess cerebral metabolic rate for glucose in infantile spasm and identified focal areas of hypometabolism, which when resected in intractable cases of spasm improved the seizure outcome considerably[10]. Focal cortical dysgenesis was the commonest identified pathology in such resected tissues[11]. This has led to postulation that focal cortical lesions serve to trigger bilateral spasms, which are likely generated at a subcortical level.

Though the proportion of symptomatic infantile spasms is expanding in the recent years, it is intriguing to realise that not all children with any of the described prenatal, perinatal or postnatal aetiology will develop infantile spasms. What predicts infantile spasm in a given aetiological category is not known. So also, what factors prognosticate the outcome in a given child with infantile spasm is a subject which needs meticulous research. Numerous factors including the clinical aspects, the EEG changes, imaging findings, the mode of therapy and the response to it, have been validated. The significance of some factors on predicting outcome are well documented, while others are of varying significance in different series. Also, data are available more often from

industrialized countries rather than from developing countries. What differences it would mean with respect to aetiology, and outcome, in a developing country needs to be documented[8].

So, as a preliminary step, we undertook to study the group of children with infantile spasms at follow up in our center, with the objective of analysing their clincial, EEG and imaging characteristics and their treatment responsiveness, and to see what bearing it has on the outcome of these children.

REVIEW OF LITERATURE

The occurrence of clusters of axial movements (spasms) in the first year of life, combined with major and subcontinuous electroencephalographic paroxysmal activity (hypsarrhythmia) is the most frequent cause of psychomotor retardation in infancy [8]. The term 'infantile spasm' denotes a specific age of onset and is therefore a syndromic concept. Because the concept usually includes hypsarrhythmia, the term 'West syndrome' should be considered more restrictive than the term 'infantile spasm'. In the 1989 revised Classification of Epilepsies and Epileptic syndromes of the ILAE, this syndrome has been said to comprise a generalised type of seizure and hypsarrhythmic EEG, and listed among both the cryptogenic and symptomatic epileptic syndromes[12]. However, at the Royamount workshop on infantile spasms, the Commission on Paediatric Epilepsy of the ILAE proposed that spasms be considered as 'a specific seizure type that involves the axial musculature and that often occurs in clusters.

Infantile spasms typically begin during the first 2 years of life, with a peak age of onset between 4 and 6 months of age. Approximately 90% of infantile spasms begin before 1 year of age, and it is rare to begin before the first 2 weeks of life, or after 18 months.

Epidemiological studies on the incidence and prevalence of infantile spasms are available (Table 1) [14].

Location	Incidence or cumulative incidence	Prevalence
1. Japan	-	1.4-1.8
2. Oklahama city	-	1.9
3. Finland	4.2	-
4. Iceland	3.0	-
5. Sweden	5.0	-
6. Rochester, MN	2.2	-
7. Atlanta	2.9	2.0

[IR - expressed as number of cases per 10,000 live births

PR - expressed as number of cases per 10,000 children at a specified time]. There is no such epidemiological study available from India.

In epidemiological surveys of childhood epilepsies, infantile spasms constitutes 1.4 to 3.9% of the total seizure types [15]. The incidence of IS has not changed much in the past two decades[16].

Pioneering effort to decipher the aetiology of infantile spasms began it 1950s and is has culminated in the segregation of West syndrome into two groups as per the latest ILAE Classification of Epilepsies and Epileptic syndromes - the symptomatic group is characterised by previous existence of brain damage signs (psychomotor retardation, neurologic signs, radiologic signs or other types of seizures) or by a known actiology. The smaller, cryptogenic group is characterised by a lack of previous signs of brain damage and of any known aetiology[13].

Some studies quote the term 'idiopathic' West syndrome as distinct from the cryptogenic group in which a hidden aetiology is presupposed. The proportion of cryptogenic/idiopathic cases varies in the reported series from 15% to 53%, probably as a result of varying definitions of the condition [17,18]. For idiopathic cases, the figures are 26% and 6% in the only two available series [19,20]. The commission on paediatric epilepsy has defined idiopathic West Syndrome by the following criteria - a. Normal development before onset of symmetric spasms, without any other kind of seizure; b. Normal clinical examination; c. Normal C.T. and M.R.I d. Recurrence of hypsarrhythmia between consecutive spasms of a cluster e. Lack of any focal interictal or ictal EEG abnormality. (Pharmacologic modification of EEG tracing may be used to confirm the latter). Idiopathic west syndioms IWS appears to result from an age-related multifactorial genetic predisposition [6].

The symptomatic group can result from a host of aetiological factors [21].

Table 2: Etiological factors associated with infantile spasms

Prenatal disorders	**Perinatal disorders**	**Postnatal disorders**
Hydrocephalus	H.I.E.	Pyridoxine dependency
Microcephaly	Meningitis/Encephalitis	Nonketotic hyperglycaemia
Hydranencephaly	Trauma	Maple syrup urine disease
Schizencephaly	Intracranial hemorrhages	Phenylketonuria
Polymicrorgyria		Mitochondrial encephalopathies

Sturge - Weber

Incontinentia pigmenti

Tuberous scleroses

Down Syndrome

Aicardi's syndrome

H.I.E

Congenital infections

Trauma

Meninitis/
Encephalitis

Degenerative disease

Neuroimaging (CT/MRI) shows abnormal results in 61% to 90% of patients, in different series [22]. The frequency of occurrence of individual aetiology varies with the type of imaging used in study series (CT/MRI) and its timing (In the age groups in which West syndrome occurs, MRI may poorly differentiate between gray and white matter, and therefore focal cortical dysplasia is often missed below 2yrs of age) [23]. H.I.E., cerebral malformations and tuberous sclerosis have been the most common aetiological factors in several large series [1,24, 25].

While a family history of epilepsy or febrile convulsions ranges from 7 to 17% of cases with West syndrome, a familial incidence of West syndrome is rarer (3% 6% in some reports) [27, 28]. Some series have noted that a family history of seizures increased the risk for infantile spasms three fold, but only in the cryptogenic group [28]. An increased frequency of DRW 52 among West syndrome patients was noted in one study, raising the possibility that immunologic mechanisms are involved in the pathophysiology; however other studies failed to substantiate this [29]. Many of the diseases associated

with symptomatic infantile spasm are heritable, accounting for some of the cases of familial West syndrome. Cryptogenic West syndrome has also been reported in monozygotic twins[30].

A hypothetical model implicating the brainstem pontine reticular formation nuclei as the unique source of both the clinical and EEG manifestations was proposed by Kellaway[9]. However, Chugani et al demonstrated abnormal foci of metabolism by FDG-PET study in children with intractable infantile spasm, which when resected, resulted in reduction of seizure frequency [10]. It was postulated that focal cortical lesions, in some way triggered or facilitated bilateral spasms, which were likely generated at a subcortical level[5]. The secondary effect on brainstem accounted for clinical spasms and for abnormal sleep activity. Shewmon proposed that focal lesion in early life produce secondary epileptogenses, leading to multifocal discharges and clinical spasms [31]. Baram et al proposed that abnormalities of the brain adrenal axis may play a role in infantile spasms[32]. Abnormality in secretion of endogenous CRH, which is a pro-convulsant neuropeptide in the immature brain, was implicated. This theory is attractive, as it offers some explanation for the ACTH responsiveness of infantile spasms. However, it needs further investigation to validate this theory.

All the above hypotheses do not confront the issue of age-dependency of infantile spasms. The normal sequence of cerebral maturation procedes from occipital to frontal, as reported by Chugani et al [33], Barkovich et al [34], Dietrich et al and Brody et al [35]. Hutten

locher et al reported increased synaptic density in the cerebral cortex in the first few months of life, followed by subsequent synaptic elimination [36]. The occipital cortex has maximum synaptic density in early infancy, and this correlates with the higher frequency of occipital structural abnormalities in early onset infantile spasms. The age of onset of spasms is delayed in frontal lesions, which mature last [38]. The initial increased inter and intrahemispheric connections in the immature brain is postulated to be the cause of bilateral diffusion of paroxysmal activity from a focal brain lesion [38].

Recently, there have been videopolygraphic studies which have documented persistence of epileptic spasms well beyond infancy [39]. This observation has been agreed upon by the commission on paediatric epilepsies (commission 1992) [6]. Spasms can be part of LGS or other symptomatic/cryptogenic epilepsies, as well.

Kellaway et al classified infantile spasms into three major groups : flexor, extensor and mixed types[24]. Intensive polygraphic monitoring has revealed that 42.50% of patients exhibit mixed spasms, while flexion and extension spasms have a frequency of 32-42% and 19-23% respectively [40]. Asymmetric spasms have been reported in different series as ranging from 10% to 25% of total cases, in its frequency [41]. They were associated with focal brain abnormality by imaging in upto 50% of such patients. As such, they are observed only in patients with symptomatic spasms. Some observed that the type of spasm sometimes changed during the same or serial recordings, raising the doubt of whether it is dependent on the child's

resting position or whether an active asymmetric tonic neck reflex can influence it[42].

Other seizures may precede, accompany or follow the onset of infantile spasm in upto 12% to 42% cases[43]. These seizures may be partial (up to 34%), genralised (upto 59%) or rarely, akinetic stare, clonic or myoclonic jerks. Partial seizures may sometimes occur at the onset of a cluster of spasms. They are mostly followed by symmetric spasms. The presence of other seizures is more frequent in the symptomatic group and often indicates a poor prognosis. On follow up 23-54% of infantile spasms evolve into Lennox - Gastaut Syndrome[44].

Psychomotor retardation very frequently accompanies the onset of infantile spasms. This may be difficult to identify in symptomatic west syndrome, because 65%- 85% of infants have preexisting mental retardation[45]. Because of the difficulty in assessing developmental normality in the first months of life the degree of regression cannot be accurately validated. Absence of psychomotor regressions is the best prognostic factor of favorable outcome [46]. Neurological abnormalities are described in 33% to 89% of patients with infantile spasm [24]. They are seen in upto 99% of patients with symptomatic spasms as opposed to 20% in the cryptogenic group (Lombroso et al) [24]. They comprise of focal motor deficits (hemiplegia, diplegia, quadriplegia), ataxia or choreoathetosis, microcephaly, blindness or deafness. In the cryptogenic group, hypotonia after the onset if infantile spasms was

the common neurological deficit noted [25].

Spasms are usually associated with markedly abnormal EEGs. Video-EEG polygraphic ictal recording is ideal to demonstrate the epileptic nature of the spasms and determine their characteristics. Sleep and awake recordings are warranted, eventually followed by intravenous administration of diazepam in search of an inter ictal focus [8]. Also recording for 24 hrs may be necessary when idiopathic West syndrome is likely. Fusco and Vigevano analysed the ictal record of 955 spasms and observed there different EEG, patterns[42].

a. An isolated slow wave, positive over vertex - central region: Often superimposed by low amplitude fast activity seen in all cases, and always corresponded to clinical spasms.

b. Spindle like activity which occurred alone or was followed by the slow wave. The main accompanying clinical manifestation was a motionless stare. This was in 35- 75% of the cases.

c. Diffuse flattening (decrementing activity) This was noted in 60% of the records only, where it always followed the ictal slow wave. No clinical manifestation accompanied it.

In addition, the background EEG in between spasms of a cluster returned to baseline hypsarhythmia in 80% of the cryptogenic group, but only in 32% of the symptomatic group. This non-return to baseline is one of the factors which predict a poor outcome.

Postictal slowing is unusual and usually the EEG quickly returns to baseline pattern [8].

Interictal EEG classically shows features of hypsarrhythmia, which was first described by Gibbs and Gibbs[3]. Hrachovy et al have analysed the interictal EEG characteristics of 290 records and reported five patterns of variation from typical hypsarrhythmia [49]. These are collectively termed 'modified hypsarrhythmia and include

i. Hypsarrhythmia with increased interhemispheric synchronization

ii. Asymmetric hypsarrhythmia

iii. Hypsarrhythmia with a consistent focus of abnormal discharge

iv. Hypsarrhythmia with episodes of generalised, regional or localized voltage attenuation.

v. Hyparrhythmia comprising primarily high voltage bilaterally asynchronous slow activity.

In prolonged video recording, more than one of the above variations may be seen in the same patient's EEG. In a study, which analysed the frequency of above variant patterns and their correlation with aetiololgy and outcome, Kramer et al found that burst suppression throughout the EEG and hemihypsarrhythmia were more likely in cerebral dysgenesis. Absence of normal sleep pattern was more frequent in patients with H.I.E.[47]. None of the hypsarrhythmic patterns had a significant association with outcome.

Inspite of significant advances in therapeutics, therapy of West syndrome remains frustrating. Only a small percentage (6%) recover

spontaneously [49]. The majority have a documented poor prognosis. Spasm may continue even till end of first decade in some. Different types of seizure disorder can emerge on follow up-partial epilepsy, L.G.S. or other symptomatic genralised epilepsy - in over 60% of the children[48]. Mental retardation (70-81%) and specific cognitive disturbances like autism & hyperkinesia (28%) are common[49, 50]. Focal motor deficits and sensory impairment persist in 35%. ACTH is the mainstay of treatment of infantile spasms, though several other AEDs have been tried. Inspite of over 30yr of its use, controlled trials are lacking. The superiority of ACTH over other steroids is not unequivocally established. Neither is the does of ACTH nor its duration of therapy is standardised. Snead et al advocated the use of high dose ACTH (150 iu/m^2/day), while Hrachovy et al administered incremental doses of ACTH from 20iu to 40iu per day[51, 52]. Riikonen et al compared the efficacy of three daily does of ACTH. 20 to 40 iu, 80iu or 120 to 160 IU and found no difference in their effect on spasms, hypsarrhythmic EEG, relapse rate or later mental development[53]. A high relapse rate (47%) after treatment and lack of definite influence on long-term outcome, as well as serious side effects are the limitations of therapy.

Vigabantrin has been evaluated as the first drug for infantile spasm in a European multi-centric retrospective survey[54]. It revealed that the response was best in tuberous sclerosis, where 96% of infants had complete suppression of spasms. The frequency of complete response was 69% in cryptogenic group and 59% in the symptomatic group excluding tuberous sclerosis. Also, when stratified for age of

onset of spasms 95% of the younger infants (onset below 3 months age) responded, as compared with 65% response in the later-onset group.

It requires controlled studies to comment on the efficacy of other AEDs (valproate, benzodiazepines etc) as first line drug for infantile spasms; more often, they are used as second line drug in patients who are refractory to steroid therapy. Surgery in the form of resection of focal lesions in intractable cases, hemispherectomy for hemimegalencephaly and uncapping of porencephalic cyst have been tried, with improvement[55, 56, 57].

Several prognostic factors have been identified the significance of which vary between deferent studies. Prognosis is directly related to aetiology [58]. Developmental delay and neurological deficits prior to onset of spasms carry a poor prognosis. Asymmetric spasms and the presence of other seizures in addition to spasms carry a poor outcome [58]. The age of onset of spasm is of doubtful significance in prognosis. Some studies noted no difference with respect to age of onset and outcome, while others noted a poorer prognosis associated with early onset of spams (below 3mo of age) [24, 25]. EEG evidence of gross asymmetry, unilateral hypsarrhythmia and focal EEG abnormalities carry a poorer prognosis, as does the lock of return of hypsarrhythmia between spasms of a cluster[59]. Abnormal neuroradiology is an important prognostic indicator in that no child with abnormal imaging was normal on follow up[59]. Several other factors which were variably associated with outcome in different series need to be validated in future.

In view of heterogeneity of the aetiology and lack of a clear concept regarding the pathophysiology and management of infantile spasms, there is a grave and justified concern for the outcome of these infants.

AIMS AND OBJECTIVES

1. To study the aetiology, clinical features, electroencephalographic and neuro imaging findings, and ACTH reponsiveness in patients with infantile spasms.

2. To study whether any of these factors significantly influence the out come and prognosis of these patients

MATERIALS AND METHODS

We had 50 cases of infantile spasm in the Department of Neurology of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, from 1994 to 1998. Five of these infatns were lost to follow up. The remaining 45 cases were directly under our care and follow up. These were the patients included in our study. The study design was a prospective follow up of a cohort selected in retrospect.

Criteria considered for inclusion of individual cases in the study were presence of infantile spasms, arrest of psychomotor development and EEG evidence of hypsarrhythmia. To define the epileptic syndrome, criterial laid down by the International League Against Epilepsy (ILAE) were adopted.

At the initial evaluation, the following data were collected - age and sex of the patient, age of onset of the infantile spasm, type of the infantile spasm, developmental and neurological status prior to the onset of the spasms, aetiological clues if any, in prenatal, perinatal and postnatal periods, presence of any other seizures before or with the onset of the infantile spasm, family history of epilepsy, current developmental status,a nd neurologic deficits if any.

The children were subjected to scalp EEG recording using the 10 - 20 international system, to procure wake and sleep records. The EEG findings were reported as typical hypsarrhythmia, defined acording to Gibbs and Gibbs (1952) or as modified hypsarrhythmia, according to the five variant patterns described by Hrachovy et al (1984). Sleep architecture was described as normal or abnormal. All the children had undergone some form of neuroimaging (CT / MRI).

The plan of treatment for these patients was a trial of injection ACTH for a period of 4 - 6 weeks at the end of which response was evaluated. The patients who received inj ACTH included some who had already been initiated on the same by the reffering pediatrician. In such cases, the dose of ACTH, and the duration of treatment were noted. The nonresponders required to be treated with other anti epileptic drugs. The choice of these alternative AEDs as well as the timing of induction of them in treatment varied from patient to patient on an individualised basis. Hence the efficacy of these individual drugs in ACTH non responders was not taken up for analysis in this study.

29 patients received the injection ACTH and 16 did not. The patients were re-evaluated after therapy and at periodic intervals during follow up ranging from one to six years at the epilepsy clinic of our institution. During follow up, the child's development and neurological status were documented . The frequency of infantile spasms if any, as well as the occurance of other seizures, was noted. The response to therapy was classified as response / inital response with later relapse / no response.

The data were analysed. Depending on historical data, the antecedent neurological - developmental status, aetiology and examination findings on admission, the subjects were divided into two groups - symptomatic and cryptogenic, as per ILAE criteria. The symptomatic group was characterised by previous existence of signs of brain damage [psychomotor retardation, neurologic signs,

radiologic signs, or presence of other types of seizures] or of a known aetiology. The eryptogenic group was characterised by absence of these features. The two groups were compared for the frequency of occurence of historical, clinical, EEG and imaging characteristic, their response to ACTH therapy, and their neurological, developmental and seizure outcome. Statistical analysis was done using the 't' test and the chi-square test. A 'p' value of less than 0.05 was considered significant.

RESULTS

Fifty children were diagnosed to have infantile spasms during the study period from Jan 1994to Dec 1998. Five of the children were lost to follow up shortly after the diagnosis and were therefore excluded from study. The study cohort therefore consisted of 45 children with infantile spasms.

Sex distribution and age of onset

There were 28 males and 17 females in this study group. (Male : female = 1.7:1). Of them, 9 patients (20%) were in the cryptogenic group and 36 patients (80%) were in the symptomatic group. There were 4 females (44.4%) and 5 males (55.6%) in the cryptogenic group; 13 females (36.1%) and 23 males (63.9%) in the symptomatic group. There was no significant difference in sex distubution between the two groups.

The age of onset of infantile spasms ranged form 1 month to 2 years in the whole cohort. The mean age of onset in the cryptogenic group (5.5 $\pm$ 3.9mo) did not differ statistically from the symptomatic group (5.7 $\pm$ 3.9mo).

The character of spasms

Spasms were symmetic in 9 (100%) of the cryptogenic group and in 35 (97%) of the symptomatic group. The type of spasms - flexor, extensor or mixed - were distributed as follows.

Type of spasm

	Extensor	Flexor	Mixed
Cryptogenic	0	8 (88.9%)	1(11.1%)
Symptomatic	2(5.6%)	30(83.3%)	4(11.1%)

Majority of the children in both cryptogenic and symptomatic groups had flexor spasms. The difference between the two groups was not statistically signifiant.

Presence of other seizrures

The presence of other seizures before, during and after the onset of spasms was seen in 20 children in the symptomatic group (55.6%) as compared to none in the cryptogenic group. The onset of other seizures preceded the onset of infantile spasms in 9 patients (45%) while the rest (55%) had other seizures after the onset of infantile spasms. The difference between the cryptogenic and symptomatic groups in this respect was of statistical significance (p=0.0 249). Generalised tonic or tonic-clonic seizures were the most frequent seizure type other than spasms.

Family history of epilepsy

This was present in 5 children (13.9%) of the symptomatic group, but in none within cryptogenic group. No child had a family history of infantile spasm. The frequency of a positive family history of epilepsy did not reach statistical significance between cryptogenic and symptomatic groups.

Development prior to onset of infantile spasm

This was definitely abrormal in 12(33%) in the symptomatic group, whereas no definite delay was noted in 24 (67%) of symptomatic group.

Birth and neonatal history

Abnormality was noted in 9 (25%) in the symptomatic group. Hypoxic - ischemic encephalpathy was the commonest perinatal event.

Clinical examination at initial evaluation

	Symptomatic	Cryptogenic
Abnormal head incumference	14 (38%)	0
Development delay	36 (100%)	8 (88.9%)
Visual inpairment	13 (36%)	0
Hearing inpairment	7 (20%)	0
Focal neurological deficit	9 (25%)	0

EEG

Interictal EEG at the initial evaluation revealed typical hypsarrhythmia in 6 patients (13.3%) and modified hypsarrhythmia in 39 (86.7%)

Neuroimaging abnormality (CT/MRI) in the symptomatic group

1	HIE	6 (16.5%)
2	Congen: brain malformation	4 (11.1%)
3	Dysmyelination	3 (8.4%)
4	Hypomyelination	3 (8.4%)
5	Cerebeal atrophy	10 (27.4%)
6	Infarction	2 (5.7%)
7	Cerebreal parenchymal calcification/others	3 (8.2%)
8	Normal	5 (13.7%)
		36 (100%)

Diffuse cerebral atrophy was the commonest imaging abnormality, followed, in frequency, by H.I.E.

The distribution of hypsarrhythmia variant patterns according to aetiology revealed no defenite association to any particular aetiology.

Aetiology		Focal epileptiform discharge	Abnormal sleep
1	HIE	3	5
2	Cong: malformation	1	3
3	Dysmyelination	0	1
4	Hypomyelination	0	1
5	Cerebeal Atrophy	2	5
6	Others	0	3
7	Normal	1	2

Eight patients (88.9%) in the cryptogenic group received ACTH injection. The remaining one patient could not afford therapy. Twenty one patients (58.3%) of the symptomatic group received injection ACTH. These children were all on low dosage schedule. The response at the end of therapy was statified as follows.

	No response	Complete response	Response but relapse	Partial response
Cryptogenic	0	2 (25%)	3 (37.5%)	3(37.5%)
Symptomatic	7 (33.3%)	2 (9.5%)	6 (28.6%)	6 (28.6%)

There were no nonresponders in the cryptogenic group, while 33% of the symptomatic group were non-responders. This difference did not reach statistical significance.

The children were tried on alternative AED when ACTH therapy failed. This included sodium valproate (44pts) clonazepam (32 pts) as the most commonly used drugs. Vigabantrin was tried in one child recently but he showed only a partial response. A single child with tuberous sclerosis in this cohort was not tried on vigabantrin. A combtination of sodium valproate and clonazepam was the most frequent among the 33 children who were on polypharmacy.

Outcome

Development

At the last follow up, the developmental status of the children was compared between the two groups

	Mild delay	Moderate delay	Severe delay
Cryptogenic	5 (62.5%)	3 (37.5%)	0
Symptomatic	8 (22.9%)	7 (20%)	20 (57.1%)

The difference in proportion of developmental delay was significant between the two groups (p=0.01219) with severe delay being observed in the symptomatic group alone.

Seizure

The seizure frequency at last follow up was compared between the two groups

	No seizure	Daily seizure	Seizure less than daily
Cryptogenic	4 (44.4%)	1 (11.1%)	4 (44.4%)
Symptomatic	8 (22.2%)	15 (47.7%)	13 (36.1%)

There was no significant difference between the groups. Six out of 36 children in the symptomatic group (12.5%) had a transition to Lennox Gastaut syndrome on follow up. They were characterised by psychomotor retardation, polymorphic seizures and EEG evidence of increased synchronisation and multifocal spikes.

DISCUSSION

Infantile spasms is an age dependent epileptic syndrome, characteristic of early childhood. Although our follow up ranges from 12 months to 72 months, it appears adequate to infer the outcome of this epileptic syndrome, in comparison with other similar studies (Koo et al 1993, Satishchandra et al)[6, 60].

In our study cohort of 45 children with infantile spasms, the symptomatic group predominated over cryptogenic group (80% vs 20%). This is an agreement with other series [Oloffoson 1995 (75% vs 25%) and Koo et al 1993 (70.2% vs 29.8%)][6,25]. Improved neuroradiological techniques have accounted for this better detection of symptomatic cases.

The age of onset of infantile spasm in our patients ranged from 1 month to 2 years (mean 5.3 months). This is cocordant with several clinical series[1,8,14,17]. There were only 3 children (6.8%) with an age of onset above 12 months. Lombroso (1983) had reported that 10% of cases had an onset beyond infancy, while Jeavons and Bower (1963) reported this in 3%[24,7]. Mean age of onset of the cryptogenic group (5.5 $\pm$ 3.4 months) was not statistically different from that of the symptomatic group (5.7 $\pm$ 3.9 months). Koo et al 1993 had the similar observation[6], while others have reported an earlier age of onset with either the symptomatic group[24] or the cryptogenic group[28]. Where the symptomatic group had an earlier onset, it was thought to even reflect the underlying structural aetiology.

The male-female ratio in our cohort of 1.7 is in accoradance with several authors who reported male - to - female ratio ranging from 2.7 (max) to 1.1(min)[24,28]. The sex distribution between symptomatic and cryptogenic group) was not statistically significant.

A higher frequency of flexor spasms was noted in our series (88%) as well as by Koo et al (1993)[25], while others had reported a premominance of mixed spasms over flexor spasms [Kellaway 1993 42% (mixed) vs. 34% (flexor); Lombroso 1983 - 50% vs 42%][24,40]. The spasms were mostly symmetric, with asymmetry being noted in 3% of the symptomatic group alone. However, other series have noted asymmetric spasms in 10% to 25% of children mainly in the symptomatic group. Because our study did not include video EEG monitoring, which is ideal for characterisation of spasms, the accuracy of the above finding could not be verified always.

Presence of other seizures before, during and after the onset of spasms was seen in[20] (55.6%) of the symptomatic group and none in the cryptogenic group in our series. This concurs with the findings of Hauser 1994[43] (38% in symptomatic group and none in cryptogenic group) and Koo 1993 (57% is symptomatic group)[6,14]. Generalised tonic or tonic-clonic seizures were the most frequent seizure type other than spasms.

Family history of epilipsy was noted in 5 children (13.9%) of the symptomatic group, but none in the cryptogenic group. None had a family history of infantile spasms, in our series. Family history of epilepsy is reported varyingly in other series ranging between 7 and 17%[27,28].

Neuroimaging (CT/MRI) was abnormal in 33(86%) cases in the symptomatic group. This is in concordance with most recent studes[22]. Hypoxic ischemic encephalopathy was the commonest aetiological factor by clinical evaluation, while diffuse cerebral atrophy followed by HIE were the most frequent imaging abnormalities. This concurs with other series[24,25].

Analysis of EEG patterns (typical versus modified hypsarrhythmia) revealed no significant difference between the cryptogenic and symptomatic groups. This is in concordance with some series (Koo 1993)[6]. When the EEG variants were stratified, hypsarrhythmia with consistent focus of abnormal discharge as well as abnormal sleep record were found exclusively in the symptomatic group. The latter reached statistical significance ($p = 0.0024$). Koo et al (1993) found no significant relationship between EEG findings and the outcome group[6], where as Kramer et al (1997) observed that burst suppression throughout the record and hemihypasrrhythmia were associated with cerebral dysgensis[47]. Abnormal sleep record with absence of normal sleep pattern was more likely with HIE. When we stratified the EEG variants according to aetiology, we did not find any significant association between a particular EEG variant and an aetiological group. In our series, we had not used any pharmacological modification (IV diazepam during EEG) which might have improved the recognition of persistent focal discharges[8].

In the present series, 29 patients had recieved injection ACTH therapy, in a low dosage schedule (20 - 40 iu/day). The duration of treatment varied according to the treatment response, but an average of 6 weeks of therapy was tried in all. There were no major complications with the above dose. The time lag to initiation of treatemnt was below 1 month is 25 children (88%). 4 children (12%) had a treatment lag of 40 -45 days. The proportion of poor cognitive outcome was not of statistical significance betwen the two groups. (early vs dealyed treatemnt). In other sereis, a shorter time lag to treatment (<1month) has ben reported to be associated with better outcome. (Singer et al 1980; Riikonen et al 1982; Lombroso 1983)[17,24,59]. The rate of relapse after initial response was 28.6% in symptomatic group and 37.5% in cryptogenic group in our series. Relapse after inital response is well documented by others as 31% (Hrachovy et al 1989) and 45%(Riikonen) ACTH responders had a better cognitive outcome as compared to non-responders, as reported by Koo et al (1993). Among patients with ACTH responsiveness, none in the cryptogenic group had a poor outcome, while 30% had a poor developmental outcome in the symptomatic group. Hence, it cannot be commented that ACTH definitely improves longterm developmental outcome. This has been observed by others as well (Hrachovy 1983)[46].

Children who did not respond adequately to ACTH were tried on alternative AEDs. Because this varied from child to child, efficacy of individual drugs was not taken up for final analysis.

Only one child in this cohort had received vigabantrin. He had a partial response, with seizure reduction by 50%.

The developmental outcome was significatly poorer in the symptomatic group when compared with the cryptogenic group (p = 0.01219) which is well documented by several series[6,24,44]. There was no statistically singificant difference in seizure outcome between the two groups. During follow up, 6(12.5%) of symptomatic West syndrome transformed into Lennox-Gastaut syndrome, while this was observed in none in the cryptogenic group[1,24,25,60].

CONCLUSION

1. Majority of the patients with infantile spasms (80%) belong to the symptomatic group.

2. Hypoxic ischaemic encephalopathy is the commonest aetiology in the symptomatic group.

3. Initial response to ACTH therapy is more marked in the cryptogenic group

4. The long-term outcome is determined more by the underlying aetiology than by the therapeutic agent used.

5. Indicators of poor prognosis are presence of other seizures and electroencephalographic evidence of persistent focal abnormality and absence of normal sleep pattern.

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