ORIGINAL ARTICLE

Clinical Spectrum of Infantile Spasm at Presentation

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ABSTRACT

Objective: To determine the clinical and EEG findings in children with infantile spasms at their initial presentation to the Neurophysiology Department, Children's Hospital, Lahore, Pakistan.

Study Design: Observational study.

Place and Duration of Study: The Neurophysiology Department, Children's Hospital, Lahore, Pakistan, from January 2008 to December 2010.

Methodology: Children aged ≤ 24 months, referred for their first EEG test was assessed for the diagnosis of infantile spasms. Clinical manifestation, EEG finding and anti-epileptic drugs being administered on presentation were analyzed by the paediatric neurologists.

Results: Among the total 2050, 410 children (20%) had infantile spasms. Mean age at presentation was 4.6 ± 3.5 months. Three hundred and twenty eight presented due to infantile spasms / seizures (80%) and 82 due to psychomotor delay / regression (20%). Seventy-two percent patients presented at the age ≤ 6 month and no patient presented after the age of 18 months. Spasm types were mixed (56%), flexors (24%), extensor (12%) and asymmetric (8%). Etiology classification was symptomatic in 58% and cryptogenic in 42%. Autonomic disturbance, impaired consciousness and abnormal eye movements were the dominant initial clinical presentations. EEG records showed hypsarrhythmic/modified hypsarrhythmic in 82% and other forms of epileptic discharges in 18%. Hormonal therapy was being administered in 12%, 40% were receiving Phenobarbitone and 34% were not being treated with any anti-epileptic agent.

Conclusion: Patients with infantile spasms have abnormal EEG findings predominantly the hypsarrhythmic modified hypsarrhythmic discharge. To avoid improper treatment, such patients should be referred to the specialized centres.

Key words: *Infantile spasms. Electroencephalogram. Neurophysiology. Hypsarrythmia. Seizures.*

INTRODUCTION

Infantile spasm (IS) is an epileptic syndrome characterized by the triad of myoclonic spasms, hypsarrhythmia on electroencephalography (EEG), and arrest/ regression of psychomotor development at onset.[1] It is divided into three etiological groups: symptomatic (secondary to brain damage), cryptogenic (probably symptomatic), and idiopathic.[2] Infantile spasm is an age-specific epilepsy syndrome, often associated with a grim prognosis in terms of epilepsy and cognitive outcome. Major obstacles to achieve significant progress in treating these patients are the relative rarity of the syndrome, their heterogeneous etiologies and the variable evolutions that limit the reported cases to small numbers with different follow-up period.

Hypsarrhythmia represents a completely chaotic and disorganized background pattern consisting of high amplitude slow waves and spikes that are asynchronous, non-rhythmic and variable in duration and topography (Gibbs and Gibbs).[3] The majority of patients present before one year of age with an incidence of 2.5 per 10,000 live births with a male predominance. Early recognition of infantile spasms and rapid control of spasms with normalization of EEG has been suggested as a good prognostic factor for long-term outcome, especially in patients with cryptogenic infantile spasms. The mechanisms responsible for the variable evolution of the seizure patterns are unknown and spontaneous remissions have been reported.[4] The relative frequency of IS among the epileptic syndromes is a reason necessitating electroencephalographic interpretation among the neuropediatricians as well as the general paediatricians. Of paramount importance is an early diagnosis, accurate clinical and laboratory examination as a prerequisite regarding prognosis and results of therapy in every single case. This would be possible only when results of large local studies are available. Although, this condition is seen in Pakistan, there has been no clinical and EEG studies of infantile spasms locally. Only a couple of studies on its treatments have been reported from Pakistan.[5,6] Due to the lack of large studies on the clinical features, EEG findings and etiological classification of IS in Pakistan.

This study was conducted to determine the same in the affected patients at their initial presentation to a paediatric neurophysiology department.

METHODOLOGY

All children aged ≤ 24 months referred to the Neurophysiology Department of the Children's Hospital,

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Lahore, for their first EEG tests, from January 2008 to December 2010 were retrospectively studied for the diagnosis of infantile spasm (IS). Diagnosis of IS was set according to international classification, and disorder was defined as a triad of symptoms: infantile spasms, specific interictal EEG pattern, and developmental delay/ regression. Diagnosis was established even if one of three elements were missing. Diagnostic work-up was tailored individually but all patients had EEG recording and neurological examinations. The spasms were classified as flexor, extensor or mixed according to Kellaway *et al.*[7] The EEG was classified as either hypsarrhythmic or modified hypsarrhythmic and other abnormalities. Besides, subjects having spasms and psychomotor retardation with multifocal, unifocal, asynchronous alternant pattern and electrical seizures on EEG were included. Interictal EEG records during cluster of spasms were captured as a electrodecremental pattern, consisting of sudden flattening of the EEG from its high-amplitude hypsarrhythmic baseline. Children, who had mimics of convulsions, but no evidence of seizures clinically and/or electrographically, were excluded.

Data were sought regarding the age at onset and the clinical types of spasms, gender, and presence of other clinical presentations, probable etiology of the spasms and commencement of antiepileptic drugs (AEDs). In all these patients, EEGs were recorded in both sleep and wakefulness.

The interictal EEG patterns were categorized into the following groups: (i) hypsarrhythmia defined as a chaotic mixture of continuous 0.75 Hz to 3 Hz slow waves, with voltages greater than 200 microvolts, and almost continuous irregular multifocal epileptic discharges in all cerebral cortical areas; (ii) modified hypsarrhythmia defined as the above EEG changes alternating with normal patterns for the age, bisynchronous slow waves and/or bisynchronous discharges; (iii) multifocal epileptic discharges: defined as focal discharges arising from two or more independent foci; (iv) discrete focal epileptic discharges and (v) asynchronous rhythmic epileptic discharges. Electrical seizures were recognized as high amplitude generalized spikes and/or slow waves followed by a period of electrodecremental activity (burst suppression-pattern), asymmetric hypsarrhythmia, localized persistent polymorphic slowing, asymmetric slowing and diffuse fast activities.[8] Commencement of AEDs was assessed verbally from caretakers or from patient's records.

Data was analyzed statistically by Statistical Package for Social Sciences (SPSS) 12. Descriptive statistics were used to find out frequencies and percentages of all the variables mentioned in the methods.

RESULTS

Over a period of 3 years, 2050 children age ≤ 2 years (18% of paediatric population age ≤ 16 years) were referred for EEG tests. Of them, 410 children (20%) had diagnosis of infantile spasm; 265 boys (64.7%) and 145 girls (35.37%) forming a male: female ratio of 1.8:1. Thirty children with hyperirritability, exaggerated response and/or colic, but no spasms or other clinical/electrical evidence of seizures, were excluded. The mean age of IS patients at presentation was 4.6 ± 3.5 months (range 1-24 months) and the mean age of the seizure onset was 3.5 ± 2.8 months. Majority (72%) of the affected children presented at ≤ 6 months of age and only 6% of these presented at > 12 months of age (Table I). Of them, 123 children (30%) had disease onset > 8 weeks before presentation. From clinical history and/or physical examination at presentation, 328 patients (80%) had spasms. Of them, 184 were mixed flexor-extensor (56%), 79 were flexor (24%), 39 were extensor (12%) and 26 were of asymmetric/ unclassified type (8%). More than one type of spasms and/or seizures occurred in 70 children (20%).

From an etiological standpoint, infantile spasms were documented as symptomatic in 190 (58%) and cryptogenic 138 (42%). All the patients had abnormal interictal and/or ictal EEG patterns. Of the total 410 patients, 40% had modified hypsarrhythmia and 30% had typical hypsarrhythmia. Ictal EEG records during the cluster of spasms were captured in 33 of these patients (8%) (Table II). In addition to seizures, eye deviation (15%) and change of face color (12%) were the most common presentations, whereas, apnea (8%) was the least frequent. Hormone therapy was being administered as the first medicine in 8% and as the second medicine in 12% of the patients. Phenobarbitone was being used in 40% while 34% children were not receiving any medicine.

Table I: Number of cases of infantile spasm in different age groups (n=410).

Age of onset in month	Number of patients	Percentage
< 3	123	30%
> 3 - ≤ 6	172	42%
> 6 - ≤ 9	65	16%
> 9 - ≤ 12	25	06%
> 12 - ≤ 18	25	06%
> 18 - 24	00	00%
Total	410	100%

Table II: EEG patterns of infantile spasms (n = 410).

EEG findings	Number of patients	Percentage
Modified hypsarrhythmia	164	40%
Typical hypsarrhythmia	123	30%
Asymmetric hypsarrhythmia	33	08%
Electrical seizures (Burst-suppression/ Electrodecremental patterns)	33	08%
Multifocal epileptic disorders discharges	29	07%
Lateralized hypsarrhythmia	16	04%
Bisynchronous rhythmic epileptiform discharges	12	03%
Normal EEG pattern for age	0	00%
Total	410	100%

DISCUSSION

Infantile spasms (IS) are the most frequent epilepsy syndrome in infancy. Approximately 90% of infantile spasms begin before 12 months of age. It is rare for infantile spasms to begin during the first 2 weeks of life or after 18 months, but this varies from country to country.[9] In USA infantile spasm constitutes 2% of childhood epilepsies but 25% of epilepsy with onset in the first year of life. The rate of infantile spasm is estimated to be 2.5-6.0 per 10,000 live births.[10,11]

This was a hospital based study, so it was not possible to calculate the incidence and prevalence in the community. Of the total 11200 patients referred for their first EEG, 2250 patients were of age ≤ 2 years, with average annual frequency of 20% in this age group. Present sampling based on 11200 children, ≤ age 16 years, referred for EEG tests over the period of 3 years, indicated an average annual frequency of 1.2%. The small percentage of IS among the total epileptic children in this study is an indicator of missing and /or delayed referral to the paediatric neurologists. However, this prevalence suggests that this form of epilepsy is not rare in Pakistani children. The male preponderance (M:F=1.8:1) is in accordance with other series.[10,12]

The index of suspicion should be high because subtle spells may initially not be recognized by primary care physicians, delaying prompt treatment.[13] The early diagnosis is of paramount importance in order to obtain even complete results in patients with so-called idiopathic situations. Similarly, in this case series, 30% had disease onset > 8 weeks before referral without any diagnosis. Majority (72%) of the patients presented at ≤ 6 months of age and only 12% presented after 12 months of age (maximum age was 24 months).

Using EEG video analysis, spasms have been categorized into three subtypes (flexor, extensor, and mixed flexor-extensor) on the basis of postural manifestations and patterns of muscle involvement during the seizure.[14] Various series give the incidence of mixed spasms as around 40-50%, flexor spasms at about 35-40% and extensor spasms at 20-25%.[15,16] In agreement the authors documented mixed spasms in 56%, flexor spasms in 24%, extensor spasms in 12% and asymmetrical/unclassified spasms in 8% of the patients. In contrast to this, Noureen and Rana documented that flexor spasms was seen in 32 (64%), extensor spasms in 8 (16%) and mixed spasms in 10 babies (20%).[17] Gaily *et al*. documented that in 12 of the 60 patients (20%), more than half of the recorded spasms were asymmetric or asynchronous.[18] This large variation in percentage of spasm types is most likely reflector of different etiologies among different case series.

The most typical finding of infantile spasm is called hypsarrhythmia, the EEG finding of a spike and wave discharge with a prominence of the slow waves.[19]

Three hundred and thirty-six patients (82%) showed interictal recordings of some pattern of hypsarrhythmia (Table II), a figure that compares favourably with literature (50-100%).[20,21] The term "modified hypsarrhythmia" is used if there is some preservation of background rhythm, significant asymmetry, or synchronous burst of generalized spike-wave activity. Some studies indicate a greater proportion of typical hypsarrhythmic recordings.[22,23] This is in contrast to the present findings of more frequent modified hypsarrhythmia (40%).

Autonomic symptom such as skin flushing, sweating, pupillary dilatation or changes in respiratory or heart rate can be present among patients who have IS.[24] Similarly, respiratory alterations, post-ictal drowsiness, abnormal eye movements and change of face colour was reported in the present patients. The etiology of infantile spasm is of primary interest for prognosis. Fifty-eight percent of the patients in study population were classified as symptomatic IS and others as cryptogenic IS, with no idiopathic case. In agreement similar findings have been documented by Zubcevic *et al*.[25]

ACTH and Vigabatrin are the only agents with proven effectiveness to suppress clinical spasms and abolish the hypsarrhythmic EEG (a specific EEG pattern found only in this syndrome) in a randomized clinical trial setting and thus remain first line treatments.[5,6,17] Despite this, 8% of the patients had received oral steroids as the first drug was used as second drug in 12% of the patients: none had received ACTH (corticotrophin) or Vigabatrin. Phenobarbitone was being administered in 40%, whereas, 34 % had received no antiepileptic agents at all. Diagnosis and treatment of infantile spasms presents a great challenge, especially in the developing countries like Pakistan, in which the diagnostic and treatment modalities are limited.

These results indicate that there is lack of the proper awareness about treatment and diagnostic options causing delayed referral to paediatric neurologist. An understanding of the mechanisms underlying the spasms will be augmented by local multi-institutional and perhaps international collaborations to obtain data with enough statistical power and to answer some of the long-standing questions in this overwhelmingly poor prognosis epileptic syndrome that presents in infancy.

CONCLUSION

Delay in diagnosis and commencement of improper anti-epileptic agents for children with infantile spasms are common despite majority of them having specific abnormal EEG findings. Therefore, there is a valid need for early referral to a paediatric neurologist or other physicians expert in the management of childhood epilepsies.

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