Original Paper

Clinical Evaluation of Infantile Spasm on a Sample of Children, Baghdad –Iraq

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Abstract

Background: Infantile spasms (IS) are a seizure disorder that was first described by William West in 1841 and has been referred to as West syndrome. It is a disorder that affects mostly those in the first year of life. Infantile spasms in most cases associated with psychomotor delay and specific pattern of electroencephalogram (EEG) pattern called hypsarrhythmia. "West syndrome" is often generally used to describe this triad.
Objective: to study clinical profile, EEG and treatment response for infantile spasm.
Patient and method: Fifty six patients with infantile spasm have been enrolled in the study who seeks medical advice from August 2015 to December 2017, conducted at the Children's Neurological Ward and Outpatient Clinics of Welfare teaching hospital, Medical City Complex, Baghdad. with onset of spasm between 1-12 month age and shows significant finding when EEG done for they and consequently at least 2 years period follow up.
Result; A total of 56 consecutive cases of infantile spasms with significant finding in their EEG were recorded; male to female ratio is 57%:43%. Structural defect in the brain was the predominant cause, 16% of children, the reason had not been proven. The Outcome was only favorable in 5 (11%) of children. Many variables like age of onset, sex, lagtimeand co-morbidity were not significant and did not affect final outcome.
***Conclusion*;** The current study highlights the clinical Evaluation of children with infantile spasm, in term of delayed diagnosis, etiology of structural brain defect, and favorable response to steroids.
Key Words: Infantile spasms, Electroencephalography, Hypsarrhythmia.

Introduction

Infantile spasms (IS) is a seizure disorder that was first described by William West in 1841 and has been referred to as West syndrome. It is a disorder that affects mostly those in the first year of life [(1)]. Infantile spasms in most cases associated with psychomotor delay and specific pattern of electroencephalogram (EEG) called hypsarrhythmia. "West syndrome" is often generally used to describe this triad [(2 and 3)].

A variety of structural abnormalities often visualized on MRI can cause infantile spasms. Additionally, variations of genetic and metabolic problems can cause infantile spasms. However, idiopathic cases of infantile spasms are not infrequent [(4)]. ISs are typically divided into cryptogenic or symptomatic. Cryptogenic type, constitutea small percent of IScase, is found in infants with uncomplicated labor and initially attained normal milestone until seizure onset, where no obvious etiology of seizure can be identified. While the symptomatic types many prenatal and perinatal insults are often blamed in most of the cases [(5)].
Despite treatment, the prognosis of West syndrome is poor with the majority (88-96%) having psychomotor retardation at follow-up [(5, and 6)]. The pathophysiology is still unknown; most ACTH effects on the central nervous system have been attributed to activation of glucocorticoid receptors. This notion is based on the fact that all of

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the entities provoking IS activate the native "stress system" of the brain. This involves increased synthesis and release of the stress-activated neuropeptide, corticotropin-releasing hormone (CRH), in limbic, seizure-prone brain regions. CRH causes severe seizures in developing experimental animals, as well as limbic neuronal injury. Steroids, given as therapy or secreted from the adrenal gland upon treatment with ACTH, decrease the production and release of CRH in certain brain regions. Second, the hypothesis that ACTH directly influences limbic neurons via the recently characterized melanocortinreceptors are considered, focusing on the effects of ACTH on the expression of CRH. Experimental data showing that ACTH potently reduces CRH expression in amygdala neurons is presented.

As the most accepted treatment modality, ACTH (adrenocorticotropic hormone) involves immunosuppression, the treatment in the same region has to be tailored to the needs of the population (exposed to increased risk of infectious diseases) [5and7].

The overall prognosis of cryptogenic WS was more serious than expected. Although the incidence of Lennox–Gastaut syndrome was low, the progression to focal epilepsy was the most common, with it appearing within the first 2 years of the diagnosis [8].

Thus, the current study was directed to describe clinical profile, seizure control,and psychological development and treatment outcomes of children with infantile spasm attending the welfare teaching hospital, medical city complex, Baghdad.

Materials and Methods

From August 2015 to December 2017, 69 consecutive patients with infantile spasm where included in a longitudinal follow-up study conducted in the pediatric neurology word and outpatient of Welfare teaching hospital, Medical City Complex Baghdad.

Inclusion criteria

1. Newly diagnosed children fulfilling the International League against Epilepsy (ILAE) for infantile spasms features [9].
2. Seizure onset from1 month to 12 months.
3. Presence of relating EEG finding.

Exclusion criteria

1. Age of onset more than one year.
2. Loss of follow up (at least 6 month).
3. nonconsenting patients.

Ethical approval

Oral consent was taken from all patient parents including in the study. The parent was informed about supposed benefit from the study prior to the agreement. Moral rules were carefully considered in all study steps.

Definitions

Psychomotor retardation or developmental delay; refers to the slow progress in attainment of developmental milestones this may be caused by either static or progressive encephalopathies[10].

Lag time; defined as the time or the duration from the onset of infantile spasms to establishment of diagnosis.

Favorable response (Seizure free) meaning: child was considered seizure-free at 28 days of age when he was free of seizures for a minimum period of 7 days. At a 3-year follow-up, a child was considered seizure-free if he had no seizures for at least the past 3 months [11].

Symptomatic infantile spasms were used for children who had a clearly defined underlying cause and/or significant developmental delay prior to the onset of spasms [12].

Classic hypsarrhythmia; is characterised by random, high- voltage spikes and slow waves. The most striking features of hypsarrhythmia are high- voltage (generally >200 μV) slow waves with variable amplitude; spikes and waves from many foci, and varying with time; and a lack of synchrony, with a generally "chaotic" appearance. The typical appearance is more likely to be found in earlier stages of ISs and when onset occurs at a younger age. The hypsarrhythmic

pattern may disappear during rapid- eye-movement (REM) sleep, but it may be found with greater sensitivity in some other stages of sleep [13 and 14].

Modified hypsarrhythmia; the presence of modified features may depend on the stage of ISs at which the EEG is performed; it may depend on treatment; and as an aggregate variable, it probably has little practical prognostic significance in randomized studies. Modified hypsarrhythmia, usually seen in the older patient, seen less disturbed to the normal background and least electrodecrements (temporary flattening of the EEG) [13].

Data inquiry

Data collected from the parent including; seizure onset, diagnosis time, spasm type, demographic data, spasm number per each cluster, average number of clusters per day, developmental milestone before and after spasm, perinatal history like birth asphyxia, history of similar or related illness in the family, etc. moreover, the examination focuses on any dysmorphic features, microcephaly, skin sigma, developmental assessment and presence of organomegaly.

Investigations work up

EEG and neuroimaging were performed for each patient included in the study. The metabolic screen is restricted to those whose history suggest an inherited or metabolic disease such as history of unexplained death, progressive or unexplained encephalopathy, unexplained vomiting, similar condition in the family, recurrent or progressive ataxia. Types metabolic workup depending on suspicion causes, including blood gas analysis, serum lactate, serum ammonia, ketene in urine, and mass spectrometry metabolic screen then high performance liquid chromatography(HPLC)to confirm the diagnosis of aminoacidopathies.

Based on the etiology, infantile spasm was classified as symptomatic (known etiology) or cryptogenic (unknown etiology).

Protocol of treatment

Available medicine options include adrenocorticoicotropic hormone (ACTH) and/or prednisolone, pyridoxine, sodium valproate, vigabatrin, clonazepam and topiramate can be used. The protocol optionin our center is steroids starting with the exception of tuberous sclerosis complex (TSC) treated by vigabatrin plus to those patient who shows unfavorable response to steroids also are treated with vigabatrin afterparents'consent,15 mg/kg/day for 3–7 days a pyridoxine trial an option for those with intractable infantile spasm. However, other treatment choices are considered consequently of sodium valproate, clonazepam and topiramate alone or in combination.

Statistical Analysis

Data were first entered in an excel file, transported later into statistical package for social sciences file version 24 (SPSS v24) for data analysis. Continuous variables were presented as means, numbers and percentages for other different variables.

The chi-square test is used to test the significant value of the correlation between discrete variables. T test for two independent variables and the Mann-Whitney testis used to signify of difference in means in independent samples.

Level of significance is set at a P value equal or less than 0.05.

Results

Fifty sixth consecutive cases of infantile spasms have been followed with significant finding in their EEG over a 2-years period. The candidates eligible for the study were 60. Two of the children was excluded for lack of adequate follow-up, and two other cases were also excluded where the initial EEG was normal. Table 1 shows the baseline characteristics of the 56children.The spasms age of onset ranged from 1 month to 10 months (mean 5.6 months). The diagnosis mean age of West syndrome was 7.8 months. The average time for treatment delay was 2.3 months. Registered children had 5.5 mean of cluster number per day.

Males formed 32 (57.1%) of the sample. The predominant type of spasm was flexor in 37 children (66.1%), then extensor in 11(19.6%) and mixed type was the least observed 8(14.3%). Majority (64.3%) did not have associated seizures, however, 18 (32.1%) were having associated focal seizures and only one was having tonic seizure and other one was having Myoclonic seizure. delay was detected before onset of spasms at 46 (82%).

The current study shows that most of the patient had symptoms [47 (84%)], structural brain defect account for 73%, the metabolic 9% and tuberous sclerosis in 2%. The etiology of the rest is not confirmed; (Table 1).

Age at diagnosis varied from 2 to 18 months with a mean age of 7.8±SD m

EEG that display the features goes with modified hypsarrhythmiaare 23 (41%) of the patient; while classical hypsarrythmiaare 12 (21%); and electrodecremental and multifocal in the rest.

Metabolic panel was performed in 48 patients and yield was positive in 9%.

Neuroimaging was fair where no obvious lesion detected only in 13patient (23.2%) and different structural defect in the rest; (Table 2).

Table 1. Descriptive statistics for sampled children**.**

Variable	Category	N	%
Age at diagnosis (m)	• Min-Max	2-18	
	• Median,Mean,SD	7.0, 7.8±3.1	
Sex	• Male	32	57.1%
	• Female	24	42.9%
Age at onset (m)	• Min-Max	1-10	
	• Median,Mean,SD	5.0, 5.6±2.1	
Lag of diagnosis (m)	• Min-Max	0-14	
	• Median,Mean,SD	1.5, 2.3±2.5	
Type of Spasm	• Flexor	37	66.1%
	• Extensor	11	19.6%
	• Mixed	8	14.3%
Clusters/day	• Min-Max	2-20	
	• Median,Mean,SD	4.0, 5.5±3.7	
Spasms/cluster	• Min-Max	1-50	
	• Median,Mean,SD	15.0, 15.3±8.7	
Associated Seizures	• Focal	18	32.1%
	• Tonic	1	1.8%
	• Myoclonic	1	1.8%
	• None	36	64.3%
Development Status	• Delayed	46	82.1%
	• Fair	10	17.9%
Comorbidity*	• Microcephaly	19	33.9%
	• Visual impairment	15	26.8%
	• Hemiplegia	5	8.9%
	• Speech delay	2	3.6%
	• Down's syndrome	1	1.8%
	• None	21	37.5%
Etiology	• Structural brain defect	41	73.2%
	• Metabolic	5	8.9%
	• Tuberous Sclerosis	1	1.8%
	• Unknown	9	16.1%
*Patients may have more than one comorbidity.			

Our study noted that about 78.2% of patients receiving steroid therapy got a favorable response with a 95% confidence interval of 64.6% to 87.8%. A favorable response under the treatment of vigapatrin was found in only two patients (28.6%) out of seven who received this drug, with a 95% wide confidence interval of 5.1% to 69.7%. However, the wide confidence interval raises a question about the importance of this observation; (Table 3).

In this study, there was no favorable response to steroid therapy associated with either sex, type of spasm, development status, or causative factors (P> 0.05) (table 4); but only significantly associated with the absence of associated seizures. Fifteen out of 17 cases associated with focal seizures got favorable response to steroid, one of the two cases associated with tonic or myoclonic seizure had a favorable response to steroids (P < 0.05): (table 4). However, this significance could be invalid because of the small sample size.

Table 2. Results of investigations done to sampled children.

Investigations	Result	N=56	%
EEG findings	• Electrodecremental	3	5.4%
	• Hypsarrythmia	12	21.4%
	• Modified hypsarrythmia	23	41.1%
	• Multifocal	18	32.1%
Metabolic Panel	• Positive	5	9.0%
	○ Folinic acid deficiency	1	1.8%
	○ Increasing serum lactate(mitochondrial disease)	1	1.8%
	○ Organic acideamia	2	3.6%
	○ Phenylketonuria (PKU)	1	1.8%
	• Negative	43	76.8%
	• Not done	8	14.3%
Neuroimaging	• Agenesis of corpus collosum	2	3.6%
	• Brain atrophy	25	44.6%
	• Unilateral encephalomalecia	7	12.5%
	• Dandy walker syndrome	1	1.8%
	• Lissencephaly	2	3.6%
	• Periventricular leukomalacia	6	10.7%
	• *Fair*	13	23.2%

Table 3. Response of infantile spasms to treatment

		Response			
Treatment		**Favorable**	**Partial**	**No response**	**Stopped***
Steroids (N=55)	n(%)	43(78.2%)	8(14.5%)	3(5.5%)	1(1.8%)
	95% CI	64.6%-87.8%	6.3%-27.2%	1.4%-16.1%	0.1%-11.0%
Vigabatrin (N=7)	n(%)	2(28.6%)	5(71.4%)	0	0
	95% CI	5.1%-69.7%	30.3%-94.9%	---	---
Other anticonvulsants (N=50)	n(%)	5(10.0%)	35(70.0)	9(18.0%)	1(2.0%)
	95% CI	3.7%-22.6%	55.2%-81.7%	9.1%-31.9%	0.1%-12.0%
Vitamins (N=4)	n(%)	0	1(25.0%)	3(75.0%)	0
	95% CI	---	1.3%-78.1%	21.9%-98.7%	---
*Stopped due to complication					

Table 4. Distribution of sample infantile spams children according to response to steroid treatment and to patients' characteristics

		Response to steroids			
		Favorable		Partial/No Response	
Variable	**Category**	**n=43**	**100%**	**n=12**	**100%**
Sex P = 0.450	Male	25	58.1%	5	45.5%
	Female	18	41.9%	6	54.5%
Type of Spasm P = 0.102	Flexor	25	58.1%	10	90.9%
	Extensor	11	25.6%	0	0.0%
	Mixed	7	16.3%	1	9.1%
Associated Seizures P = 0.035*	Focal	15	34.9%	2	18.2%
	Tonic	0	0.0%	1	9.1%
	Myoclonic	0	0.0%	1	9.1%
	None	28	65.1%	7	63.6%
Development Status P = 0.669	Delayed	36	83.7%	8	72.7%
	Fair	3	7.0%	1	9.1%
	Normal	4	9.3%	2	18.2%
Etiology P = 0.549	Structural	36	83.7%	10	90.9%
	Idiopathic	7	16.3%	1	9.1%
*This P value could be invalid. Expected cell count in this sub-table is less than one.					

The study found that patients who had a favorable response to treatment were significantly older on average than those who had a partial / no response (8.1 m compared to 6.0 m) (P <0.5), and there was no significant effect for age at onset (5.8 m compared to 4.5), lag of diagnosis (2.3m compared to1.5 m), clusters/day (5.5compared to5.9), and spasms/cluster (15.8compared to14.5) upon the response to treatment for steroids (P > 0.05).

There was no significant correlation between the presence of sequelae of complications for both sexes, presence of associated seizures and causes of spasms (P > 0.5) ;(table 5). This study found a significant correlation between the complicated disease and associated seizures (taking into account that all associated focal seizures have complications) but this significance is still being questioned due to small sample size constraints.

The outcome was not significantly affected by any of age at diagnosis, age at onset of disease, lags of diagnosis, clusters a day, or spasms per cluster according to this study (P > 0.5).

Discussion

The onset of infantile cramps (5.6 months) in the current study was similar to other studies [14 and 15]. The average delay in starting treatment in most Western studies is within the range of 25 to 45 days [15]. The lag time in this study was much greater, possibly due to the lack of orientation of this type of seizures between the general physician who usually saw the patient for the first time and unfortunately sometime prescribes of unsuitable antiseizure like carbamazepine, phenobarbitone and phenytoin, however yet compatible with the study of developing countries [16]. Interestingly, the study reveals that there is no significant association of lag time with outcome. Many studies show contrast finding, and this display a good outcome with early diagnosis and treatment [17 and 18]. However, another study showing the same result [16], this discrepancy may be related to the size of the sample.

Table 5. Distribution of sample infantile spasm children according to outcome and to studied characteristics

	Outcome				
	Complication		**Fair**		
Variable	**N=50**	**100 %**	**N=6**	**100%**	**P value**
Sex					0.618
• Male	28	56.0%	4	66.7%	
• Female	22	44.0%	2	33.3%	
Age at diagnosis (m);Mean±SD	7.8±3.1		8.2±3.4		0.778
Age at onset (m);Mean±SD	5.6±2.1		5.7±2.9		0.910
Lag of diagnosis (m);Mean±SD	2.2±2.6		2.5±1.6		0.797
Clusters/day;Mean±SD	5.3±3.2		7.5±6.4		0.167
Spasms/cluster;Mean±SD	15.4±8.7		14.8±9.2		0.886
Type of Spasm					0.438
• Flexor	32	64.0%	5	83.3%	
• Extensor	11	22.0%	0	0.0%	
• Mixed	7	14.0%	1	16.7%	
Associated Seizures					**0.012***
• Focal	18	36.0%	0	0.0%	
• Tonic	1	2.0%	0	0.0%	
• Myoclonic	0	0.0%	1	16.7%	
• None	31	62.0%	5	83.3%	
Etiology					0.063
• Structural brain defect	39	78.0%	2	33.3%	
• Metabolic	3	6.0%	2	33.3%	
• Tuberous Sclerosis	1	2.0%	0	0.0%	
• Unknown	7	14.0%	2	33.3%	
*This P value could be invalid. Expected cell count in this sub-table is less than one.					

We found slight male preponderance in our study, these results are similar to some other studies, but males dominate them [16 and 19], while another study showed contrast of result as females are predominant [20], therefore our male predominance consider fair in comparison. The interesting finding in our study was preceding seizure where third of them initially experience focal seizure then proceed to infantile spasm, this can be related to the structural defect in the brain of whatever reasons that make up tow third of etiology.

Thepercentage of symptomatic type of infantile spasm in present study is greater than to study done in United Kingdom, symptomatic spasm were detected in 61% of the patients, while in this study, 84% of the cases have symptomatic causes[21], however its compatible with Indian study[16],this could be related to advanced supportive measure prenatally, perinatally and postnatally.Vision, hearing impairment and microcephaly are the most common associated comorbidities of structural brain defect in infantile spasm patient. However, this study did not observe the effect of these comorbidities on the end result.

Our study showed that 82% of children had preceding developmental delay before onset; epileptic encephalopathy before seizure onset is attributed to supposed etiology. This is slightly lower than Indian study [16]. Therefore, psychomotor delay prior to the presentation is not considered being symptomatic infantile spasm.

Electrodecremental EEG, burst_ suppression and less spectacular ictal EEG commonly encountered in infantile spasm as well as the classical interictal hypsarrhythmia and if it's asymmetrical usually suggest structural focal lesion in the brain. Nevertheless, the absence of hypsarrhythmia doesn't exclude the diagnosis of infantile spasm and even doesn't preclude the initiation of treatment, as the hypsarrhythmia or other EEG finding are represent a dynamic process that may

appear at any stage of coarse of infantile spasms[22].

This work might be reviewed because all infants did not have the same detailed investigations, for instance metabolic panel investigation done in 48(85%) patient and the yield was 5(9%) had metabolic disease and this consider interesting in such rare cause of infantile spasm(it's not done routinely to all patient and restricted to metabolic suspicion cases), however, treatable conditions such as phenylketonuria, organic acidurias, cerebrospinal fluid (CSF) glucose in GLUT 1 deficiency (Glucose Transporter Deficiency syndrome), pyridoxine dependency should be considered at least in those who fail to respond promptly to treatment in addition to folate and B12 metabolic disorders, because they are treatable.

The neuroimaging reveals 77% have a defect in brain structure and thus MRI becomes an important tool of assessment for those infants who no etiology have been identified yet. Sometimes a cranial CT scan may be required as a preferred initial option to exclude TSC, since the diagnosis of calcification in TSC can be difficult to detect by MRI in young children.

The response to steroid in our study was encouraging with a favorable response of 78%, and this treatment is still a gold standard compared to other parameter and guidelines (except for vigabatrin for the infantile spasms associated with tuberous sclerosis complex), and this is

Similar to many study [23–24]. Unfortunately, corticosteroids are also more likely to have a higher rate of side effects and one patient stop treatment because of the adverse effect.

The study found that patients with a favorable response to treatment were significantly older on average than those who had a partial / no response. I do not know if this is strongly linked to the disease, that the more severe cases will be diagnosed earlier than the other.

Overall, most our patient were poor, with 75% having developmental delay, often moderately to severe and 14% developing epilepsy, For many years, it was often reported that the only factor influencing cognitive outcomes later was the underlying etiology of the infantile spasms, with those who have bad symptomatic etiologies doing bad, and this constant result is not found in our study. The treatment did not significant impact on the outcome and this is similar to the Indian study [16].

Conclusion

We describe the clinical profile of children with infantile spasm. Prolonged lag time between spasms onset and treatment initiation. The most common cause of the disorder is the structural brain defect. There was no statistically significant relationship between all variables and unfavorable results in this study.

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