Original Article

Treatment Outcome of Infantile Spasms in Neurology Clinic at Wah Cantt

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ABSTRACT

Objective: To analyse the treatment outcome of cases with infantile spasms presented in Paediatric Neurology clinic at POF Hospital and Izzat Ali Shah Hospital Wah Cantt.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Neurology clinic at POF Hospital and Izzat Ali Shah Hospital, Wah Cantt and we consecutively enrolled patients with infantile spasms from a period of 12 months from 1st July 2017 to 30th June 2018.

Materials and Methods: All patients with infantile spasms who presented in Paediatric neurology clinic were analysed. Primary outcome was the improvement in spasms after 6 months of treatment. Treatment was given as Prednisolone, Vigabatrin or combination of both. Data like gender, age of onset of spasm, spasm type, aetiology, developmental delay, head size, pathology, EEG findings, neuroimaging results and outcome in the form of improvement was recorded. Data was analysed in SPSS version 19.

Results: Total 25 patients were studied, 64% of them were male and age of first spasms was < 6 months in 72% of cases. Spasm type was flexor in 56% of the children, 80% of the children had symptomatic type of spasms with development was delayed in 76% of the cases. Hypoxic ischemic encephalopathy was the main pathological cause (40%), Brain atrophy was the commonest finding on neuroimaging and modified hypsarrythmia was found in EEG in 52% of cases. Most of the patients (n=13) were given prednisolone trial and>80%improvement in spasms was seen with all the treatment but combination therapy was mostly effective (60%), though it was not statistically significant. Vigabatrin was effective in patients with Tuberous sclerosis complex.

Conclusion: In our study infantile spasms mostly affected males with symptomatic type and associated with developmental delay. Combination therapy of Prednisolone and Vigabatrin was found to be the most effective treatment. Vigabatrin is an effective treatment in cases of Tuberous sclerosis.

Key Words: Infantile Spasms, Tuberous sclerosis, Prednisolone, Vigabatrin

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INTRODUCTION

Infantile spasms (IS) is a rare age-specific type of seizure, which occurs in West syndrome, A characteristicEEG appearance called hypsarrhythmia and a high risk of severe developmental delay are other features of the syndrome.[1] The onset of these characteristics spasm typically seen between 4 to 7 months.[2]These seizures typically present with a triad of lightning (involving the entire body), nodding (convulsions of the throat and neck flexor muscles) and Salaam or jackknife attacks (rapid bending of the head and torso forward and simultaneous raising and bending of the arms) Infantile spasms are distinct from myoclonic and tonic seizures. They are characterized by a contraction phase followed by a more tonic phase. The contraction phase may be a flexor spasm, extensor spasm, or a combination of both and these could be symmetrical or asymmetrical.[3]The etiology is variable and includes cortical malformations, neurocutaneous syndromes, inherited metabolic disorders, perinatal brain injuries (asphyxia, hypoglycemia, sepsis, and meningitis), and postnatal acquired brain injuries such as meningitis and head trauma.[2] Based on etiology, West syndrome is classified as symptomatic with known etiology andidiopathic (unknown etiology).[4] Infantile spasm is an age-specific epilepsy syndrome, often associated with a poor prognosis in terms of epilepsy and cognitive outcome. Infantile spasms may present in different ways. There may be single episodes rather than clusters [Infantile spasms single-spasm variant (ISSV)], Hypsarrhythmia without infantile spasm (HWIS) and infantile spams without hypsarrhythmia (ISW).[5]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-

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up period.[6]Because of the poor response rate, a wide variety of drugs are used to treat IS the world over. However, two commonly used forms of therapy are adrenocorticotrophic hormone (ACTH) and prednisolone (or prednisone). More than 40 years ago, ACTH was used empirically to treat these seizures with some success and later on oral steroids were tried as well.[1]In the last decade, Vigabatrin has been shown to be the first anticonvulsant to have a significant response rate for infantile spasms but serious visual field defect has been found in approximately one-third of treated adults and is known to occur in children.[7]The treatment of infantile spasms has been quite a challenge for the Paediatric neurologist as the entity appears to be resistant to many conventional antiepileptic drugs. Agents that have been used in the treatment of infantile spasms include Benzodiazepams (especially Nitrazepam), Sodium Valproate, Vigabatrin (VGB), Corticosteroids, ACTH, Ketogenic diet, Vitamin B6, intravenous Gammaglobulin, a Benzodiazepam-Carbamazepine combination, topiramate and zonisamide etc.[7]Vigabatrin is available in Europe but not readily in many countries including Pakistan. There is some evidence that excess of corticotrophin releasing hormone (CRH) may be the common pathway for the development of seizures in the developing brain[7].

MATERIALS AND METHODS

Many children with poorly controlled seizures are referred to our Paediatric Neurology clinics at POF hospital and Izzat Ali Shah Hospital, WahCantt. We studied the clinical profile of patients diagnosed with infantile spasms. This was a cross sectional study. The diagnosis of IS was made when child presented with characteristic seizures (flexor or extensor spasms, eye deviation alone or in combination) and in addition EEG showed hypsarrhythmia or one of its variants.[1] All patients diagnosed with IS on basis of history of characteristic salaam spasms as described above and had been followed up for 6 months oncetreatment was started, were included in the study over 12 months period from 1st July 2017 to 30th June 2018.The following data from the patients obtained: gender, age of onset of infantile spasm, spasm type, aetiology, developmental delay, head size, pathology, EEG and neuroimaging findings, and response to treatment in the form of improvement which was >80%, 50 to 80% or <50% reduction in spasms as judged by the parents. Patients were given Prednisolone, Vigabatrin or combination of both. Oral prednisolone was given as 2mg per kg per day for 4 weeks followed by tapering in next 2 weeks except for the patients diagnosed with TSC. Children receiving oral prednisolone were seen at 2-week intervals in Paediatric Neurology clinic. Blood sugar, urine analysis and stool for occult blood were performed whenever indicated. Because of lack of free availability and cost issues ACTH was not given to any patient. Vigabatrin was given in a starting dose of 15 to 20 mg/kg/day which was increased up to maximum of 70 mg/kg/day. In combination therapy, Prednislone was given with a dose of 2 mg/kg/day for first two weeks and then Vigabatrin was added. Later Prednisolone was tapered off but Vigabatrin was continued.

RESULTS

Total 25 patients were included in the study from the Paediatric neurology follow up clinic. Table 1 shows that 16 (64%) children were male and 9 (36%) were female. Eighteen (72%) patients had their first infantile spasm prior to age of 6 months. Flexor type of infantile spasms was the predominant clinical type in 56% of patients (n=14). Twenty (80%) patients were classified as symptomatic infantile spasm. Developmental delay was noted in 19 (76%) patients. Microcephaly was found in 14 (56%) patients. Hypoxic ischemic encephalopathy (HIE)was the main diagnosis in 10 (40%) children while Tuberous Sclerosis (TSC) was found in 9 (36%) patients.All cases of HIE exhibited microcephaly with head size < -2 SD. Neuroimaging showed brain atrophy in 10 (40%), periventricular leukomalacia in 3 (12%), calcification in 4 (16%), tubers in 2 (8%) and other findings in 6 patients. Encephalomalcia were significant findings in patients with HIE. Patients with TSC typically had sub-ependymal calcifications and tubers on neuroimaging along with neurocutaneous stigmata, rest of the patients were either normal or had subtle atrophy on brain scans. Nine (36%) patients exhibited classically psarrhythmia, thirteen (52%) showed modified hypsarrhythmia and 3 (12%) showed other findings on EEG.

Regarding treatment all patients except those with TSC were given prednisolone or combination therapy. TSC patients received Vigabatrin, 3 of those patients responded well while 2 patients had partial response (Table 2). Two patients lost to follow up. Out of 13 patients who were given prednisolone alone, 5 (38%) showed improvement in reduction of spasms, while 4 (30.8%) showed partial improvement (50-80%). Four (38%) patients fail to respond and two of them developed signs of steroid toxicity and prednisolone had to be stopped. Five patients received combination of Prednisolone and Vigabatrin therapy and 3 (60%) patients had >80% improvement. P value is 0.170, which is not statistically significant.

Valproic acid, Clonazepam, Levetiracetam and Topiramate were used as adjunct therapy in study. Patients in study are still in follow up in neurology clinic, apart from seizures these patients also having other problems like delayed speech, aggressive behavior, neuropsychiatric issues and autistic behaviour etc.

Table No.1: Demographic and clinical factors associated with infantile spasms

	Frequency(n)%
Gender	
male	16(64.0%)
female	9(36.0%)
Age at first spasm	
<6months	18(72.0%)
6-10 months	6(24.0%)
>10 months	1(4.0%)
Spasm type	
Flexor	14(56.0%)
Extensor	3(12.0%)
Mixed	8(32.0%)
Aetiology	
Idiopathic	5(20.0%)
Symptomatic	20(80.0%)
Developmental delay	
Normal	6(24.0%)
Delayed	19(76.0%)
Head size	
Microcephaly	14(56.0%)
Normal	11(44.0%)
Pathology	
Hypoxic ischaemic encephalopathy	10(40.0%)
Tuberous Sclerosis	9(36.0%)
Normal	2(8.0%)
Other	4(16.0%)
Neuroimaging	
Brain atrophy	10(40.0%)
Periventricular Leukomalcia	3(12.0%)
Calcification	4(16.0%)
Tubers	2(8.0%)
Other	6(24.0%)
EEG Findings	
Classical Hypsarrhythmia	9(36.0%)
Modified Hypsarrhythmia	13(52.0%)
Other	3(12.0%)

Table No.2: Treatment of infantile spasms with improvement outcome

	Improvement					
	>80 (n)%	50-80 (n)%	<50 (n)%	Lost to follow up (n) %	N	P value
Prednisolone	5(38.5%)	4(30.8%)	4(30.8%)	0(0.0%)	13	0.170
VGB	3(42.9%)	2(28.6%)	0(0.0%)	2(28.6%)	7	
Combination	3(60.0%)	1(20.0%)	1(20.0%)	0(0.0%)	5	

DISCUSSION

This study was descriptive cross sectional study from the neurology clinic of POF hospital and Izzat Ali Shah Hospital. POF hospital is a social security type hospital and is responsible to provide health care facilities to serving/retired POF`s employees and families/ parents of the employees.Izzat Ali Shah is a welfare hospital and provide patient care in subsidized rates. Most patients included in the study were the local residents of area. In our study males were more involved than femalesi.e 64% which was comparable to 63% males in study done by Ibrahim S et al[7]. The reason being, males are given more access to health facility due to socioeconomic factors. Symptomatic infantile spasms was the main classification type found in our study in more than 80% patients while Malik MA et al found 58% symptomatic IS and 42% idiopathic IS[4]. HIE was documented as main pathological feature in our study which was comparable to studies done by Azam M et al (36%) and Ibrahim S (69.4 %)[1,7]. Nine (36%) patients exhibited classical hypsarrhythmia comparable to Malik MA (30%)[4].

Regarding treatment most of our patients given the trial of prednisolone as it was cheap, easily available and relatively better tolerated than ACTH and amongst those 13 patients most of them responded well to steroid therapy. Azam M et al concluded that there was no significant difference between two modes of therapy in a resource depleted country like Pakistan[7]. Initially, it was thought that prednisone was as effective as ACTH[8,9]. More recently, it has been shown that ACTH is superior to 2 mg/kg/day prednisone and high dose is no better than low-dose ACTH[10]. The 2 mg/kg/day dose of prednisone has been suggested to be too low in the Cochrane review[11], though they are not satisfied with overall quality of RCTs done so far as sample is small and methodology is poor[12]. ACTH is expensive, given parenterally and may be difficult to obtain in some countries: synthetic ACTH (tetracosactide) is beginning to replace the natural product. Prednisolone, on the other hand, is inexpensive, given orally and is easily available.[1] Vigabatrin is specifically effective in treatment of infantile spasms in patients with Tuberous sclerosis complex (TSC), but unfortunately, reports of serious visual field defects have led to a significant reduction in the use of the drug[13]. According to Harekar[14]and Mackay[15], ACTH was found to be the most effective treatment. However, in view of the cost of ACTH, Harekar suggested oral prednisolone either alone or as a follow-up after termination of ACTH therapy[14]. In our study we conclude that VGB is effective medication in patients with TSC which is comparable to studies done by Parisi P et al[13]and others[16,17]. A famous UKISS study also found prednisolone and tetracosactidebeing more effective in controlling infantile spams as compared to Vigabatrin

at young age[18]. More over these hormones can be choice of treatment after failure of Vigabatrin therapy[19]. Steroids are not as effective after 12 months of age[20]. In our study we tried combination therapy, where high dose prednisolone was given for 2 weeks and then Vigabatrin was added and later prednisolone was tapered off. More than 50% improvement was seen in 80% of the patients which is better than prednisolone alone (69%). There is no comparative study available. Further work on combination therapy with bigger sample size needs to be done.

CONCLUSION

Infantile spasms are more prevalent in males and Hypoxic ischemic encephalopathy is the major cause. Most of the children exhibit developmental delay. Steroids are preferred mode of therapy however more trials are required with ACTH therapy in our patients as its being internationally recommended. VGB is effective treatment in patients with TSC. Combination of Prednisolone and Vigabatrin is an effective mode of therapy in most cases of Infantile spams. Further studies are required with bigger sample size.

Author's Contribution:

Concept & Design of Study:	Tahir Mahmood, Shahzad Haider
Drafting:	Tahir Mahmood, Shahzad Haider
Data Analysis:	Shahzad Haider
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