ECRONICON OPEN ACCESS

EC NEUROLOGY
Research Article

Comparative Study on Infantile Spasms in Upper and Lower Egypt

Ibrahim Shoukry[1], Heba El Awady[2]* and Maha MA Abo Hashish[3]

[1]*Pediatrics Department, Cairo University, Egypt*

[2]*Pediatrics Department, Fayoum University, Egypt*

[3]*Department of Pediatrics, National Research Center, Egypt*

***Corresponding Author:** Heba El Awady, Pediatrics Department- Fayoum University, Egypt.

Received: October 17, 2017; **Published:** April 17, 2018

Abstract

Background: Infantile spasms (IS) are unique disorder of infancy and early childhood. The average age at onset is 6 months and the average incidence is approximately 0.31 per 1000 live births. Awareness of IS is globally increasing in the majority of Egyptian provinces. Early diagnosis and early initiation of treatment has a favorable prognosis. The study compares between different possible etiology, clinical presentation, imaging and outcome of cases with IS in Lower Egypt and Upper Egypt. It also highlights the response of spasm to early initiation of Vigabatrin (VGB).

Patients and Methods: 117 cases of IS presented in the first year of life were retrospectively reviewed. They were divided into two groups according to their residence as Upper Egypt and Lower Egypt group. History, clinical data, EEG, brain imaging and response to antiepileptic drugs were compared between the two groups.

Results: Upper Egypt group (Group 1) comprised 24 cases (20.5%) and Lower Egypt group (Group 2); 93 cases (79.5%). Consanguinity was 75% in group 1; and 45% in group 2. Microcephaly was encountered in 50% of cases of group 1 and in 25% in group 2. Brain MRI abnormalities were detected in all cases (100%) in group 1 and in 77.4% of cases in group 2 (abnormalities included increased signal intensity, ventriculomegaly, agenesis of corpus callosum and cortical dysplasia). Evidence of hypoxic ischemic encephalopathy was present in 75% in group 1 and 25.8% in group 2. EEG showed hypsarrhythmia/modified hypsarrhythmia (75% in group 1 and 45% in group 2). Focal epileptogenic discharges were recorded in 12.5% in group 1 and 22.6% in group 2. Molecular studies identified two mutations in Lower Egypt group; CDKL5 and KCNO2.

Conclusion: Increasing awareness in primary health care providers regarding IS will result in better seizure control and psychomotor development. We strongly recommend initiation of VGB in treatment of IS for better and faster control of seizures. Molecular studies for cases with IS may help in better prediction of outcome and subsequent prenatal diagnosis.

Keywords: *Electromyography; Spasm; Hypsarrhythmia; Development; Molecular*

Abbreviations

EEG: Electroencephalography; MRI: Magnetic Resonance Image; IS: Infantile Spasm; TSC: Tuberous Sclerosis Complex; VFD: Visual Field Defect; VGB: Vigabatrin

Introduction

Infantile spasms (IS) are epileptic spasms that occur in infancy or early childhood. These spasms are classically characterized by symmetric, brief jerking spells of the head, neck, arms, legs, and abdomen. These spasms may consist of flexion, extension, or a combination of flexion-extension. Infantile spasms often are associated with a characteristic pattern on electroencephalogram (EEG) called hypsarrhythmia [1].

The primary treatment objective is to improve the EEG and stop the spasms as soon as possible and to avoid prolonged treatment durations with any form of therapy [2]. The American Academy of Neurology and Child Neurology Society practice parameter published in 2004 (updated in 2012) concluded that adrenocorticotropic hormone (ACTH) and vigabatrin (VGB) should be considered standard treatments for infantile spasms [3]. Some infants clearly respond better to combination therapy than to hormone treatment alone. Response rates dropped in those initiating treatment greater than 2 months after spasm onset [4]. However, VGB is an effective treatment of infantile spasms that controls spasms of all etiologies in about 50% of patients when used as monotherapy [5]. Some treatments, including topiramate and ketogenic diet, seem promising besides adrenocorticotropic hormone, steroids, and vigabatrin [6].

Patients and Methods

One hundred and seventeen cases of IS presenting in the first year of life were retrospectively reviewed. They were divided into two groups, according to their residence, as Upper Egypt and Lower Egypt group. Cairo and the governorates north to it are the Lower Egypt group whereas governorates south to Cairo are the Upper Egypt one.

Each group is further subdivided, according to the age of onset of presentation, to cases presented above six months of age and cases presented below six months of age. Consanguinity, head circumference and presence of clusters were reviewed. Etiologies were divided into structural malformations, hypoxic ischemic encephalopathy or unidentified. EEG was done for all cases and findings were recorded as hypsarrhythmia and epileptogenic discharges whether focal or generalized. Brain MRI was done for all patients.

Statistical Methods

Microsoft excel 2010 was used for data entry. IBM SPSS (statistical package for social science) version 21 (SPSS Inc., Chicago, IL) was used for data analysis. Simple statistics such as frequency distribution and comparisons were used. Relationship for qualitative data was displayed in cross tabulations and Comparisons of proportions were performed using the chi-square and Fisher's exact tests. A p value less than 0.05 was considered statistically significant.

Results

Data belonging to all cases in this study were tabulated and statistically analyzed (Table 1). Subsequently, cases were classified according to their residences into two groups (Table 2). Upper Egypt group (Group 1); 24 cases (20.5%) and Lower Egypt group (Group 2); 93 cases (79.5%). Group 1 to Group 2 ratio was 1:4. Sex distribution among cases in group1 was 1.6:1 in favor of male sex. Sex distribution in group 2 was 1:1. However, this had no statistical significance (P value= 0.340). First cousin parents were reported in 75% in group 1; and 45% in group 2. Upper Egypt group had a significant higher consanguinity rate than Lower Egypt group (P value= 0.009). Caesarian section was reported in 75% of cases in group 1 and 61% in group 2. This had no statistical significance (P value= 0.212). Age at first presentation was less than 6 months in 87.5% in group 1 and 77% of group 2. This had no statistical significance (p value= 0276). Developmental delay was reported in 87.5% in group 1 and 80.6% in group 2. This had no statistical significance (P value= 0435).

		Frequency	%
Age at presentation	Less than 6 months	93	79.5
	More than 6 months	24	20.5
Sex	Male	63	53.8
	Female	54	46.2
Residence	Upper Egypt	24	20.5
	Lower Egypt	93	79.5
Mode of Delivery	Normal Vaginal	42	35.9
	Cesarean section	75	64.1
Consanguinity	+ve	60	51.3
	-ve	57	48.7
Aetiology	Structural Malformation	24	20.5
	Hypoxic Ischemic Encephalopathy	42	35.9
	Unidentified etiology	51	43.6
Head circumference	Microcephaly	36	30.8
	Normal	81	69.2
Developmental Milestones	Delayed	96	82.1
	Normal	21	17.9
Spasm Clusters	Present	60	51.3
	Not present	57	48.7
EEG findings	Hypsarrhythmia	33	28.2
	Modified Hypsarrhythmia	27	23.1
	Suppression Burst	12	10.3
	Epileptogenic discharges	24	20.5
	Normal	21	17.9
MRI findings	Increased Signal Intensity	18	15.4
	Ventriculomegaly	39	33.3
	Agenesis of Corpus Callosum	9	7.7
	Cortical Dysplasia	30	25.6
	Normal	21	17.9
VGB administration	Yes	105	89.7
	No	12	10.3
Cessation of spasms	Yes	66	56.4
	No	51	43.6
Identified Gene mutation		2	1.7

Table 1: *Demographic data and clinical and radiological workup for the studied group.*

	Upper Egypt	Lower Egypt
Number of Cases	24 (20.5%)	93 (79.5%)
Sex distribution Male :Female	1.6:1	1:1
First cousin parents	75%	45%
Delivery by cesarean section	75%	61%
Age of presentation < 6 months	87.5%	77%
Microcephaly	50%	25%
Brain MRI (Structural malformation)	12.5%	22.5%
Hypoxic ischemic encephalopathy	75%	25.8%
Identified Gene mutation	Not done	2.2%
Unidentified etiology	12.5%	49.5%
EEG: Hypsarrhythmia	75%	45%
EEG: Focal epileptogenic discharges	12.5%	22.6%
Response to Vigabatrin	50%	58%

Table 2: *Comparison between Infantile spasms in Upper Egypt and Lower Egypt.*

Microcephaly was encountered in 50% of cases of group 1 and in 25% in group 2. Microcephaly was noted to be significantly higher in Upper Egypt group than in Lower Egypt group (p value = 0.022). EEG was done for all cases in this study showing hypsarrhythmia/ modified hypsarrhythmia in all cases with infantile clusters (75% in group 1 and 45% in group 2). Focal epileptogenic discharges were recorded in 12.5% of cases in group 1 and in 22.6% in group 2. EEG abnormalities were insignificantly more reported in Lower Egypt group than in Upper Egypt (p value = 0.435).

Evidence of hypoxic ischemic encephalopathy was present in 75% of cases in group 1 and in 25.8% in group 2. While structural brain malformations were reported in 12.5% of cases in group 1 and 22.5% of cases in group 2. These difference in etiologies between Upper and Lower Egypt groups showed statistical significance (P value = 0.001). Brain MRI abnormalities were significantly more detected in Group 1 (100%) than in Group 2 (77.4%); (P value = 0.010).

Molecular studies identified two mutations in Lower Egypt group; CDKL5 and KCNO2. No molecular was done for any of the Upper Egypt group due to high costs. Etiology of IS remained unidentified in 12.5% of cases in group 1 and 49.5% of cases in group 2.

Complete cessation of seizures with initiation of Vigabatrin was encountered in 50% of cases in group 1 and 58% in group 2. This showed no statistical significance (P value= 0.052). Adding on other AEDs such as Topiramate and Sodium valproate in intractable cases noticeably reduced the frequency of spasms and the duration of the clusters in both groups. Trial for initiation of Ketogenic diet gave initial good response. However, intolerability was a major complaint which lead to poor compliance. Hormonal therapy with ACTH was considerable alternative to VGB but edema was a common side effect and relapse was reported in many cases after cessation of injection.

Discussion

The higher incidence of IS in this study in Lower Egypt more than in Upper Egypt was related to easier access to Cairo from the Delta than from Upper Egypt. In our comparative study, almost equal sex distribution was noted in Lower Egypt group. Similarly, Zupanc [7] found no significant gender difference in IS. In a study by Tripathi and Patel [8], a positive history of consanguinity was present in 6.3% of IS and family history of seizures was present in 14.8% of cases. First cousin parents were more reported among Upper Egypt (75%) than in Lower Egypt (45%) because of rural closed communities. Ninety percent of IS begin in infants younger than 12 months. Peak onset is at age 4 - 6 months [7]. In this study, early age of first presentation (less than 6 months of age) was more reported in Upper Egypt group. This may be due to the more severe presentation noticed in Upper Egypt group driving parents to seek medical advice at early stage. Cases with

IS secondary to hypoxic ischemic encephalopathy were more observed in Upper Egypt where secondary and tertiary care for deliveries are less developed. Microcephaly was the most common finding in a study of IS by Tripathi and Patel [8], (50.5%). In the current study, microcephaly was encountered in 50% of cases of group 1 and in 25% in group 2.

Regarding EEG findings, hypsarrhythmia (Figure 1) was encountered in all cases with clusters and was more common in Upper Egypt group (58% vs 50%), whereas focal epileptogenic spikes (Figure 2) were more common in Lower Egypt group (22.6% vs 12.5%). Tripathi and Patel [8], reported 84.2% of children with IS had hypsarrhythmia, 10.5% had generalized seizure discharges and 4.2% patients had normal EEG.

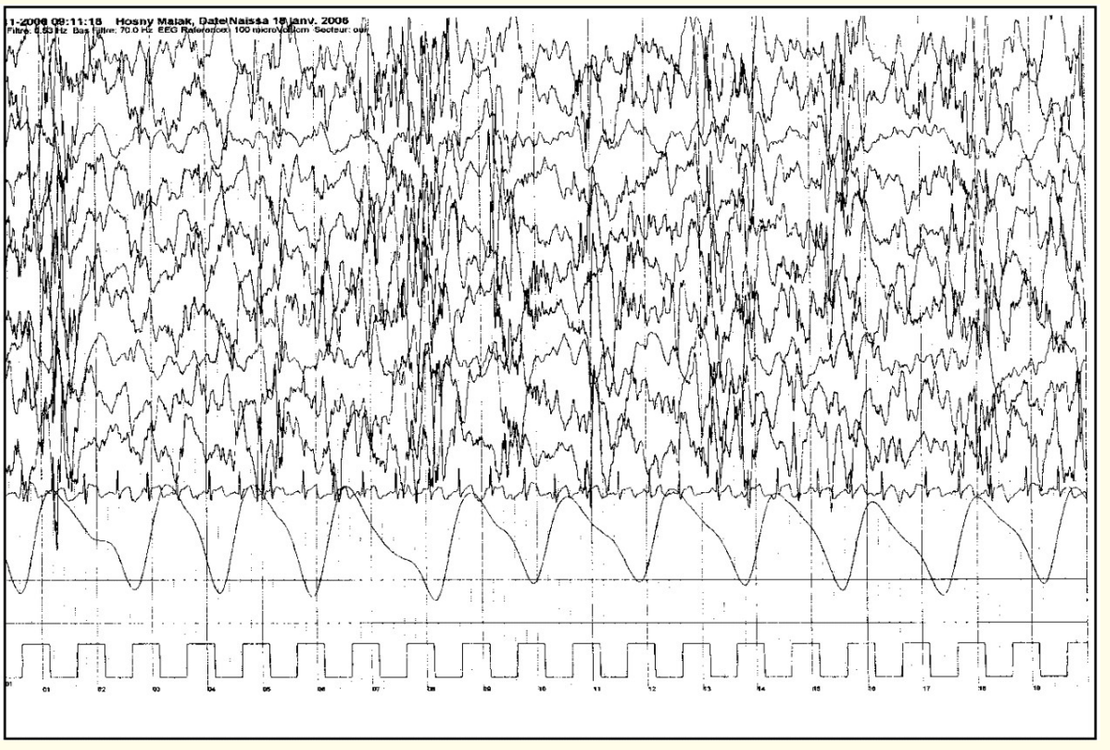

Figure 1: *EEG showing hypsarrhythmia.*

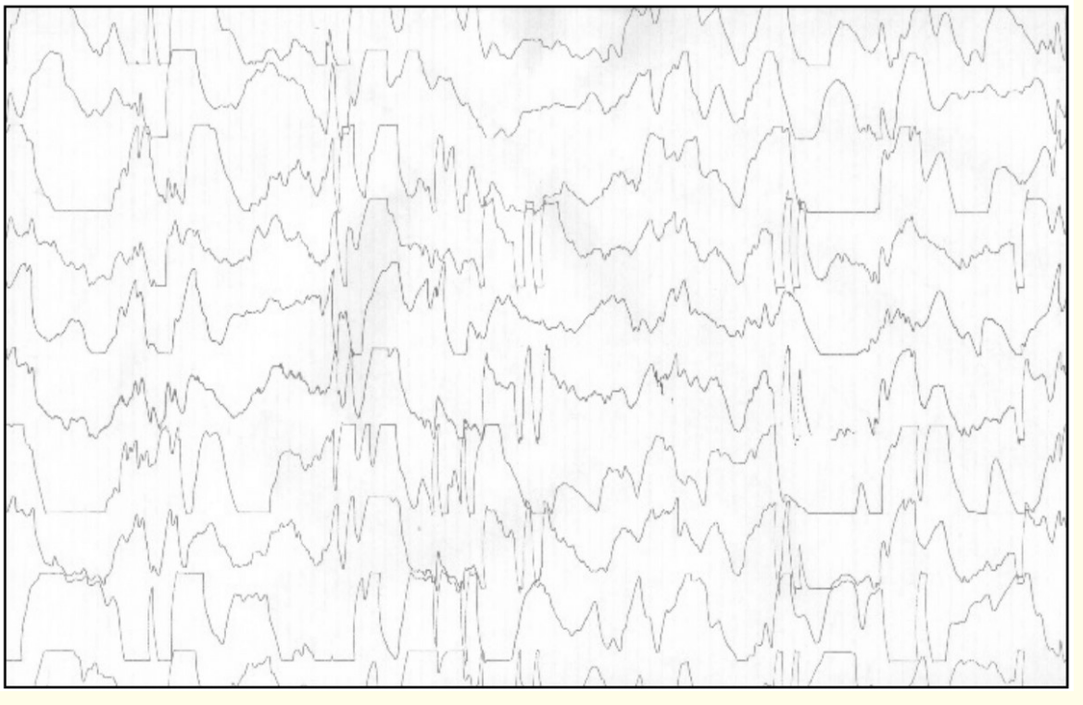

Figure 2: *EEG showing multifocal epileptogenic discharges.*

Etiology can be identified in 70% or more of patients with IS and it is expected that this will continue to improve with more widely-available genetic testing. However, brain MRI remains the study with the highest yield in identifying etiology [9]. Mary., *et al*. [10] reported brain MRI abnormalities in 62% of cases with IS. These abnormalities included cerebral malformation (hemimegalencephaly, schizencephaly, lissencephaly, holoprosencephaly, corpus callosal agenesis as part of Aicardi syndrome and altered gyral morphology), hydrocephalus, cerebral atrophy, old infarcts, cystic encephalomalacia, extensive calcification, bilateral thalamic hyperintensities and nonspecific white matter hyperintensities, and tuberous sclerosis complex (TSC) with multiple cortical tubers. In our study, structural brain malformations were more commonly observed in Lower Egypt group (22.6% vs 12.5%). These abnormalities included cortical dysplasia, agenesis of corpus callosum, nonspecific white matter high signal intensities, cerebral atrophy, areas of encephalomalacia.

In this study, two mutations were identified in Lower Egypt group; CDKL5 and KCNO2. Archer., *et al*. [11] reported that CDKL5 mutations are a significant cause of infantile spasms and early epileptic seizures in female patients, and of a later intractable seizure disorder, irrespective of whether they have suspected Rett syndrome. Fehr., *et al*. [12] evaluated the phenotype of 77 girls and 9 boys with early-onset encephalopathy due to CDKL5 mutations. The disorder was characterized by seizure onset usually before 3 months of age, severely impaired gross motor, language, and hand function skills, and subtle but shared dysmorphic features.

Regarding management, ample evidence has been provided to support the use of VGB in the treatment of IS, and for many years European neurologists have considered VGB to be the drug of choice for the symptomatic treatment of IS [13-16]. Used as a first line of treatment in monotherapy, the percentage of children who are rendered seizure-free averages around 50% [17]. Efficacy is lower in refractory cases, but still approaches total control in 30% of children [18]. TSC represents a particularly successful story for the use of VGB, since the drug controls spasms in up to 95% of patients [18]. Higher VGB doses correlate with shorter times to response rates. Its most serious side effect is retinal toxicity characterized by visual field defect (VFD) [5]. It has been suggested that VFDs are a result of vigabatrin inhibiting taurine uptake in the gastrointestinal tract, leading to taurine deficiency-related retinal toxicity [19]. In our comparative study, response to VGB was encountered in 50% of cases in group 1 and 58% in group 2. On serial follow up of visual field, neither cases in group 1 nor group 2 showed any signs of retinal toxicity or visual field defect. Similarly, in a recent study of Japanese patients with infantile spasms, VGB was well tolerated for the duration and extent of exposure with no observed peripheral VFDs [20].

Conclusion

Comparing IS in Upper and Lower Egypt; we find that consanguinity play a more important role in Upper Egypt. IS is more related to hypoxic ischemic encephalopathy and microcephaly in Upper Egypt. Structural brain malformation should be considered in cases presented with IS. In both groups, IS is presented as early as 6 months of age. Etiology can be identified in 50% or more of patients and it is expected to be improved with more widely-available genetic testing which will help in better prediction of outcome. Our study is one of few Egyptian studies that support the initiation of VGB as a monotherapy in treatment of IS for better and faster control of seizures with no reported side effects. Increasing awareness in primary health care providers regarding IS will result in better seizure control and psychomotor development.

Acknowledgment

Authors would like to thank all patients and their families for participating in this work. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

None.

Bibliography

1. Kathryn L., *et al*. "Spasm, Infantile (West Syndrome)". Treasure Island (FL): StatPearls Publishing (2017).

2. Hrachovy RA and Frost JD. "Infantile spasms". *Handbook of Clinical Neurology* 111 (2003): 611-618.

3. Go CY., *et al*. "Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society". *Neurology* 78.24 (2012): 1974- 1980.

4. O'Callaghan FJ., *et al*. "Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial". *Lancet Neurology* 16.1 (2017): 33-42.

5. Camposano SE and Thiele EA. "Vigabatrin in the Treatment of Infantile Spasms Infantile Spasms". *US Neurology* 5.2 (2010): 82-84.

6. Song JM., *et al*. "Efficacy of Treatments for Infantile Spasms: A Systematic Review". *Clinical Neuropharmacology* 40.2 (2017): 63-84.

7. Zupanc ML. "Infantile Spasm". *Expert Opinion on Pharmacotherapy* 4.11 (2003): 2039-2048.

8. Tripathi V and Patel A. "Clinical profile and outcome of children with infantile spasms, from a single centre registry study at Concept Paediatric Neurology Centre, Ahmedabad, India". *European Journal of Pediatric Neurology* 19.1 (2015): 15-2318.

9. Gary Rex Nelson. "Management of infantile spasms". *Translational Pediatrics* 4.4 (2015): 260-270.

10. Mary Iype., *et al*. "Ahamed: Infantile spasms: A prognostic evaluation". *Annals of Indian Academy of Neurology* 19.2 (2016): 228-235.

11. Archer HL., *et al*. "CDKL5 mutations cause infantile spasms, early onset seizures, and severe mental retardation in female patients". *Journal of Medical Genetics* 43.9 (2006): 729-734.

12. Fehr S., *et al*. "The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy". *European Journal of Human Genetics* 21.3 (2013): 266-273.

13. Wheless JW., *et al*. "Vigabatrin". *Neurotherapeutics* 4 (2007): 163-172.

14. Parisi P., *et al*. "Current role of vigabatrin in infantile spasms". *European Journal of Paediatric Neurology* 11.6 (2007): 331-336.

15. Desguerre I., *et al*. "The management of infantile spasms". *Archives of Disease in Childhood* 93.6 (2008): 462-463.

16. National Institute for Health and Care Excellence. Clinical guideline 137. Epilepsies: diagnosis and management (2016).

17. Riikonen R. "Infantile spasms: therapy and outcome". *Journal of Child Neurology* 19.6 (2004): 401-404.

18. Camposano SE., *et al*. "Vigabatrin in the treatment of childhood epilepsy: a retrospective chart review of efficacy and safety profile". *Epilepsia* 49.7 (2008): 1186-1191.

19. Riikonen R., *et al*. "Does vigabatrin treatment for infantile spasms cause visual field defects? An international multicentre study". *Developmental Medicine and Child Neurology* 57.1 (2015): 60-67.

20. Yoko Ohtsuka. "Efficacy and safety of vigabatrin in Japanese patients with infantile spasms: Primary short-term study and extension study". *Epilepsy and Behavior* 78 (2018): 134-141.

Volume 10 Issue 5 May 2018