http://www.banglajol.info/index.php/JNINB

Original Article

DOI: https://doi.org/10.3329/jninb.v8i2.63747

Journal of National Institute of Neurosciences Bangladesh,
July 2022, Vol. 8, No. 2, pp. 130-135

ISSN (Online) 2518-6612
ISSN (Print) 2410-8030

Clinical and Electroencephalographic Pattern and Short-Term Outcome to Treatment in Infantile Spasm: A Randomized Controlled Trial

Most. Samsun Nahar Sumi[1], Razia Sultana[2], Sufia Khatun[3], Mohammad Shah Jahan Chowdhury[4], Mohammad Enayet Hussain[5], Rajib Nayan Chowdhury[6], Narayan Saha[7]

[1]Junior Consultant, Department of Pediatric Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [2]Senior Trainer and Consultant, Bangladesh Pratibondhi Foundation, Dhaka, Bangladesh; [3]Junior Consultant, Department of Pediatric Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [4]Medical Officer, Department of Pediatric Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [5]Associate Professor, Department of Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [6]Professor and Head, Department of Neurophysiology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; [7]Professor and Head, Department of Pediatric Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh

[**Received on:** 22 April 2022; **Accepted on:** 12 May 2022; **Published:** 1 July 2022]

Abstract

Background: Infantile spasms (epileptic spasm) is an epileptic encephalopathy with unique clinical and electrographic features, which affects children mostly in the middle of the first year of life. **Objective:** The aim of this study was to evaluate the clinical and electroencephalographic profile and short-term outcome in infantile spasm. **Methodology:** This was a randomized controlled trial study done in Department of Pediatric Neurology, National Institute of Neuroscience & Hospital, Dhaka, Bangladesh. The patient of infantile spasm aged 2 months to 2 years were enrolled in the study from June 2017 to May 2018. With parent's written informed consent, they were randomized into two groups, 25 in each. One group got ACTH only and another group got both ACTH and vigabatrin. Detailed history including seizure pattern was taken. EEG was done before and after2 -3 weeks of starting treatment. They were followed up at 8, 15, 43 days. **Results:** The mean age of onset of seizure (mean ±SD) was 7.24±4.13 (2 to 19) month on hormonal therapy and 6.84±5.89 (2 to 22) month on combination therapy. Most patient had history of perinatal birth asphyxia, developmental delay, seizure pattern was flexor spasm and EEG pattern were predominantly classical hypsarrhythmia in both groups. After treatment cessation of spasms occurred between 14 to 42 days in 72.0% in combination therapy and 44% in hormonal therapy (P value=0.045). EEG became normal in 60.0% and 32.0% patients in combination and hormonal therapy respectively (P value =0.047). **Conclusion:** In conclusion combination therapy of ACTH hormone plus vigabatrin has better than ACTH therapy alone in cessation of clinical spasms and electroencephalographic remission. *[Journal of National Institute of Neurosciences Bangladesh, July 2022;8(2):130-135]*

Keywords: Infantile spasm; ACTH; hypsarrhythmia

Correspondence: Dr. Most. Samsun Nahar Sumi, Junior consultant, Department of Pediatric Neurology, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh; **Email:** nahardrsamsun@gmail.com; **Cell No.:** +8801791252525; **ORCID ID:** https://orcid.org/0000-0001-6300-4672

Conflict of interest: There is no conflict of interest relevant to this paper to disclose.

Funding agency: This research project was partially funded by Bangladesh Medical Research Council (BMRC)

Contribution to authors: Sumi MSN, Sultana R, Khatun S, Saha N were involved in protocol preparation, data & sample collection and literature search and manuscript writing. Chowdhury MSJ, Hussain ME, Chowdhury RN were involved in sample preparation and testing.

How to cite this article: Sumi MSN, Sultana R, Khatun S, Chowdhury MSJ, Hussain ME, Chowdhury RN, Saha N. Clinical and Electroencephalographic Pattern and Short-Term Outcome to Treatment in Infantile Spasm: A Randomized Controlled Trial. J Natl Inst Neurosci Bangladesh 2022;8(2):130-135

Introduction

Infantile spasms constitute a severe infantile epileptic syndrome that is difficult to treat and is associated with a poor outcome[1]. Normal neuro-developmental regression occur with the onset of this devastating disorder and delayed treatment can lead to worse outcome[2-5]. Infantile spasms are a form of severe epilepsy that affects approximately 2-3.5/10,000 live birth and commonly

affects under 1 year with a peak age of onset 4 to 7 months[6]. West syndrome is a devastating form of epilepsy defined by a triad of infantile spasms, hypsarrhythmia and developmental regression[7]. The classic spasm type referred to as an epileptic spasms is characterized by symmetric, bilateral, brief contraction of the neck, trunk and extremities[8]. Less commonly, they consist of an extensor spasm of the legs and spine or simple head nodding[9]. Rarely they are asymmetrical.The seizures (spasms) that characterize infantile spasms are highly variable in appearance, but they typically occur in clusters,commonly 20 or as many as 100 spasms can occur in a single cluster.

Individual spasms generally last between 0.5 and 10 seconds and repeat every 5 to 30 seconds in clusters of approximately 2 to 20 minutes10. These clusters frequently occur as the infant is awaking from sleep[10]. In most cases, they resolve by the age of three, although rarely can persist up to 10 to 15 years of age[11]. Approximately two-thirds of affected infants will have a detectable underlying neurological abnormality, Infantile spasms have been classified as symptomatic, cryptogenic or idiopathic[8]. Prenatal etiologies include central nervous system malformations, chromosomal abnormality (trisomy 21), single –gene error (ARX, CDKL5/STK9), neurocutaneous syndromes, congenital central nervous system infections, and rarely inborn error of metabolism. Prenatal precipitants include hypoxic ischemic encephalopathy and hypoglycemia. And postnatal factors include intracranial hemorrhage, acquired central nervous system infections. In infantile spasm, EEG is severely abnormal. The EEG pattern of the "chaotic rhythm," hypsarrhythmia was described in the 1950s by Frederic and Erna Gibbs as a continuously abnormal pattern of very-high-amplitude (often up to 500 μV) with asynchronous slow waves and multifocal spikes and polyspikes[12]. This was later expanded by Kellaway and others into modified forms such as increased interhemispheric synchronization, hemihypsarrhythmia, and hypsarrhythmia characterized by predominantly slow waves, discontinuous records, and focal abnormalities[13].

The seizures are refractory to treatment with most conventional antiepileptic drugs. The current first line treatments options are corticosteroid either adrenocorticotropic hormone natural ACTH or synthetic Tetrasacosactoid or Prednisolone and vigabatrin. Although the spasms resolve with time, the long –term prognosis is poor. Many children develop other forms of severe epilepsy like Lennox-Gastaut syndrome and most (80.0% to 90.0%) have psychomotor retardation[13-14]. This study was undertaken to evaluate the clinical and electroencephalographic profile and short-term outcome in infantile spasm.

Methodology

Study Settings and Population: This randomized controlled trial was done in outdoor and indoor in Department of Paediatric Neurology at National Institute of Neurosciences and Hospital (NINSH), Dhaka, Bangladesh during the period of June 2017 to June 2018.

Randomization and Blinding: After taking ethical permission, with parent's written consent, participants were randomly assigned (1:1) by lottery method, 25 children in each group.

Allocation: The study enrolled 50 patients aged 2 months to 24 months who had a clinical diagnosis of infantile spasms and a hypsarrhythmia (classical or modified hypsarrhythmia) in EEG. Detailed history and through examinationwere done in every child. Tuberous sclerosis, infantile spasm mixed with other seizure type, neurometabolic diseases, previously treated with steroid or vigabatrin or ACTH were excluded. One group was treated with natural Adrenocorticotrophic hormone alone by intramuscular injection. Dose of Natural ACTH was 150IU/m2/day BD×2 wks then taper off for another 2 weeks. Another group of children was treated with combination therapy. Combination therapy i.e. hormonal therapy with vigabatrin therapy: ACTH and vigabatrin was given simultaneously. ACTH was given as same dose mentioned above. Vigabatrin was given orally 100mg/kg in 2 divided doses for three months then taper off for another 1 month.

Follow Up and Outcomes Measures: The primary outcome was cessation of spasms from 14th day to 42 days after initiation of therapy. Electroencephalography (EEG) was done within 14 to 21 days after starting of treatment. Parents filled a daily record of spasm frequency for the first 42 days of the trial and follow up was done in every child on 7, 15, 43 days.In this study responders were considered those who became spasms free from day 14 to 42 after .starting treatment and non-responder who were not spasm free between day 14 to day 42. After getting treatment short-term outcome was considered the follow-up period for 42 days.

Statistical Analysis: Data was collected in a pre-designed questionnaire with informed written consent and were presented in graph and tabulated form. Finally analyzed by SPSS and probability values of <0.05 was considered as statistically significant.

Results

There was no significant difference between the 2 treatment groups in terms of age and sex. Mean age at randomization was 11.28±5.19 (3-22) month in hormonal therapy and 9.72±5.1 (3-24) months on combination therapy (Table 1).

Table 1: Mean with SD of Age of the Patients in Two Groups (n=50)

Age	Groups		P Value
	Hormonal Therapy	Combination Therapy	
Mean±SD (Range)	11.28 ±5.19 (3 to 22)	9.72 ± 5.4 (3 to 24)	[a]0.220

[a]Mann-Whitney U test was done to measure the level of significance

The sex distribution was almost equal in both groups (Figure I).

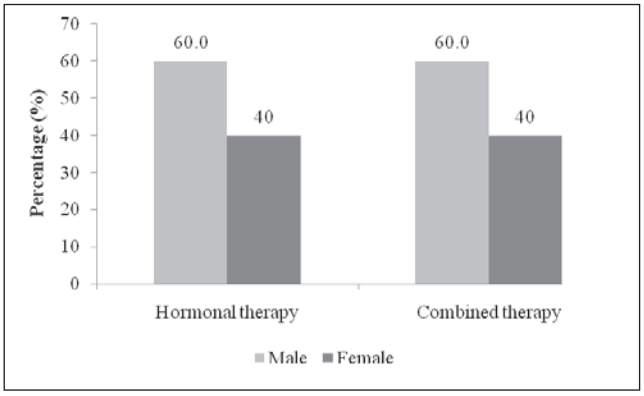

Figure I: Sex distribution in both groups

The mean age at onset of epilepsy was 7.24±4.13 month on hormonal therapy and 6.84±5.89 months on combination therapy. Flexor type of spasm was most common in both groups. Frequency of seizure before starting treatment (mean ± SD) was 10.04 ± 5.57 times on hormonal therapy and 10.24 ± 6.20 time on combination therapy (p=0.899). There was no significant difference in relation to age of onset of seizure and frequency of seizure between two groups (p>0.05) (Table 2).

Table 2: Seizure characteristics of the patients in groups (n=50)

Seizure Characteristics	Groups		P Value
	Hormonal Therapy	Combination Therapy	
Age of onset of seizure (months) [mean±SD]	7.24 ± 4.13 (2-19)	6.84 ± 5.89 (2-22)	[b]0.278 [b]0.899
Frequency of seizure [mean±SD]	10.04 ± 5.57	10.24 ± 6.20	
Type of Spasms			
• Flexor	25 (100.0)	24 (96.0)	[a]1.000
• Extensor	0 (0.0)	1 (4.0)	

[a]Fisher's Exact test was done to measure the level of significance; bMann Whitney U test was done to measure the level of significance

About 25(100%) children had history of perinatal asphyxia on hormonal therapy and 24(96.0%) on combination therapy. About 96.0% had history of developmental delay on hormonal therapy and 80.0% on combination therapy. History of perinatal birth asphyxia was absent in only one case in combination therapy group. Family history of epilepsy was absent in hormonal therapy group and present in 8% of cases in combination therapy group. There was no significant difference in relation to development history between two groups (p>0.05) (Table 3).

Table 3: Clinical parameters of the patients in groups (n=50)

Clinical Parameters	Groups		P Value
	Hormonal Therapy	Combination Therapy	
H/O Perinatal Birth Asphyxia			
• Absent	0(0.0%)	1 (4.0%)	1.000
• Present	25 (100.0%)	24 (96.0%)	
H/O Neonatal Septicaemia			
• Absent	25 (100.0%)	24 (96.0%)	1.00
• Present	0(0.0%)	1 (4.0%)	
Family History Epilepsy			
• Absent	25 (100.0%)	23 (92.0%)	1.000
• Present	0(0.0%)	2 (8.0%)	
Development history			
• Age appropriate before seizure	1 (4.0%)	5 (20.0%)	0.182
• Delayed	24 (96.0%)	20 (80.0%)	

Fisher's Exact test was done to measure the level of significance

EEG before therapy was found as classical hypsarrhythmia in 68.0% cases on hormonal therapy and 60.0% cases on combination therapy. There was no significant difference in EEG findings between two groups (p>0.05) (Table 4)

Table 4: EEG before Therapy of the Patients in Groups (n=50)

EEG	Groups		P Value
	Hormonal Therapy	Combination Therapy	
Classical hypsarrhythmia	17(68.0%)	15(60.0%)	0.556
Modified hypsarrhythmia	8(32.0%)	10(40.0%)	

Chi square test was done to measure the level of significance.

Changes in Outcome variable following intervention: After treatment patient became spasm free from 14 days to 42 days (n=18, 72%) in combination therapy and (n=11, 44%) in hormonal therapy. [OR 0.306, 95% CI 0.094-0.992, p=0.045]. Responder was significantly high in combined therapy than that of hormonal therapy (Table 5).

Table 5: Cessation of spasm of the patients in groups (n=50)

Cessation of spasm (14 – 42) days	Groups		P Value	OR (95%CI)
	Hormonal Therapy N (%)	Combination Therapy N (%)		
Responder	11 (44.0)	18 (72.0)	0.045	30.6%
Non responder	14 (56.0)	7 (36.0)		(9.4-99.2)

Chi square test was done to measure the level of significance.

EEG became normal after getting treatment for 2 to 3 weeks in 15 (60.0%) children on combination therapy and 8 (32.0 %) children on hormonal therapy. So electroclinical response was better in combination therapy. EEG found normal significantly higher in combined therapy group compare to hormonal therapy group ($p<0.05$) (Table 6).

Table 6: EEG Response of the Patients after Treatment for 2 to 3 weeks in groups (n=50)

EEG	Groups		P Value
	Hormonal Therapy	Combination Therapy	
Normal	8(32.0%)	15(60.0%)	0.047
Abnormal	17(68.0%)	10(40.0%)	
Total	**25(100.0%)**	**25(100.0%)**	

Chi square test was done to measure the level of significance

Discussion

Infantile spasm is a catastrophic, agespecific epilepsy syndrome with unique clinical and electrographic features that has its onset within the first 12 months of life[15]. This disorder is characterized by epileptic spasms which consist of massive myoclonic jerks of the body, which can be extensor or flexor (or both) in nature. Infantile spasms often are accompanied by developmental regression and a characteristic interictal electroencephalogram (EEG) pattern known as hypsarrhythmia.

In this study, mean age at randomization (mean age ± SD) was 11.28±5.19 month in hormonal therapy and 9.72±5.1 months in combination therapy. Onset of spasm occurs most often between the ages of 3 and 12 months, although onset has been reported as late as childhood and even adulthood and males predominate (60%-70%)[16]. The mean age at onset of seizure in our study was 7.24 ±4.13 month in hormonal therapy and 6.84±5.89 month in combination therapy which was similar to other studies. A Cochrane review of infantile spasms showed that the mean age at spasm onset was given in seven studies and ranged from 5 to 7 months.16Our study showed a male predominance with the sex ratio being 3:2 which was consistent with other study. One study also showed the mean age of onset being 5.65 months with slight male preponderance (58.5% vs. 41%)[17].

The seizures (spasms) that characterize infantile spasms are highly variable in appearance, but they typically occur in clusters and often commence upon awakening. Spasms have generally been described as flexor forced anterior flexion of the neck and axial musculature, often with concomitant elevation and extension of the bilateral upper extremities, extensor forced extension of the head and neck, or mixed flexor/extensor. In our study most common type of spasm was flexor 100% in hormonal therapy group and 96.0% in combination therapy group and second common cause was extensor type of spasm 4.0% in combination therapy group. Another study showed (79.2%) of cases presented with flexor spasms, (8.9%) with extensor spasms and (11.9%) with mixed spasms[14]. Among the several pre-, peri- and postnatal insults responsible for epileptic spasm, adverse perinatal events are the most important causes. In this study, most of children had developmental delay (96% in combination therapy group, 80% in combination therapy group) and we found perinatal asphyxia was the most prevalent cause (100.0% in hormonal therapy, 96% in combination therapy) and second cause was neonatal septicemia (4.0% in combination therapy). In another study showed that history of perinatal asphyxia was present in 38.5% cases[17]. ICISS study showed that risk of developmental impairment was 55.0% in combination therapy and 54% in hormonal therapy and risk of

developmental impairment was chromosomal abnormality, cerebral palsy, neonatal encephalopathy[18]. These findings are indicative of lack of awareness and poorer maternal and neonatal health services in developing countries as compared to that of developed countries.

For confirm the diagnosis of infantile spasm EEG is needed.The EEG has the characteristics of hypsarrhythmia, a disorganized interictal pattern that consists of random high-voltage slow waves and spikes. In addition to classic EEG pattern, there are several hypsarrhythmia variants, which have been grouped together and termed as "modified hypsarrhythmia". In this study showed that EEG before therapy was found as classical hypsarrhythmia in 68% on hormonal therapy and 60% on combination therapy.Another study showed EEG we found modified hypsarrhythmia in most of the cases (57%) followed by hypsarrhythmia (28.6%) and multifocal discharges (10%)[17].

The current first-line treatment options for infantile spasms are corticosteroids-either adrenocorticotrophic hormone (natural ACTH or synthetic tetracosactride) or vigabatrin especially for Tuberous Sclerosis. In this study combination therapy (ACTH and vigabatrin) compared with hormonal therapy alone was associated with more infants achieving the primary outcome of spasm cessation between days 14 to 42 days.In this study cessation of spasm occurred in 72% on combination therapy and 44.0% in hormonal therapy which was similar to ICISS study (OR0.306, [95% CI 0.094-0.992], p=0.045). ICISS study showed that the primary outcome was assessed in 377 infants and cessation of spasm occurred in 72% infants on combination therapy and in 57% infants on hormonal therapy (difference 15.0%, 95% CI 5.1-24.9, P=0.002)[18]. A Cochrane review of infantile spasms had determined that hormonal treatment was the best single treatment for the cessation of spasms[19]. Several prospective, randomized trials of ACTH or cosynotropin of varying doses have shown 42% to 87% of patients experienced cessation of spasms within 2 weeks of initiating therapy and Hypsarrhythmia resolved in 20% to 90% of patients[20]. High –dose ACTH(60IU/day or 150IU/m2 has been associated with excellent short-term response rates (87%-93%) in prospective studies20Hrachovy and coworkers found no difference between high dose and low dose[21].UKISS study (United Kingdom Infantile study) reported that hormonal therapy (either synthetic ACTH or corticosteroids) stopped the spasms in 73% of infants after 2 weeks, compared with vigabatrin in 54%.[20] Other investigators have also found that combination therapy might be the most effective way of treating severe epilepsy syndromes in childhood[22]. The goal of treatment is to prevent the encephalopathy by stopping the spasms and improving the EEG background EEG became normal after 2 weeks in 60% in combination therapy and 32% in hormonal therapy. ICISS study showed that electroclinical response was achieved in 66% in combination therapy and 55% in hormonal therapy.

There are several limitation of study. Sample size was small. Necessary investigations could not be done for searching aetiology of infantile spasm due to economic constraints.

Conclusion

In conclusion age of onset of epileptic spasm was 2 months to 2 years. Most patient had history of perinatal birth asphyxia, developmental delay and flexor type of spasm. EEG pattern was predominantly classical hypsarrhythmia in both groups. Combination therapy was better in cessation of spasm along with EEG remission than hormonal therapy alone.

References

1. Pavone P, Striano P, Falsaperla R, Pavone L, Ruggieri M. Infantile spasms syndrome, West syndrome and related phenotypes: what we know in 2013. Brain and Development. 2014;36(9):739-51.
2. Illingworth RS. Sudden mental deterioration with convulsions in infancy. Arch Dis Child 1955 39:529–37.
3. Koo B, Hwang PA, Logan WJ. Infantile spasms: Outcome and prognostic factors of cryptogenic and symptomatic groups. Neurology. 1993; 43(11):2322-2327.
4. Kivity S, Lerman P, Ariel R, Danziger Y, Mimouni M, Shinnar S. Long-term cognitive outcomes of a cohort of children with cryptogenic infantile spasms treated with high-dose adrenocorticotropic hormone. Epilepsia. 2004 ;45(3):255-262.
5. O'Callaghan FJ, Lux AL, Darke K, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, Verity CM, Osborne JP. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. Epilepsia. 2011; 52(7):1359-1364.
6. Pellock JM, Hrachovy R, Shinnar S, Baram TZ, Bettis D, Dlugos DJ, Gaillard WD, Gibson PA, Holmes GL, Nordli DR, O'Dell C. Infantile spasms: a US consensus report. Epilepsia. 2010; 51(10):2175-2189.
7. Gibbs FA,Gibbs EL.Atlas of Electroencephalography. Cambridge, MA: Addison. Wesley;1952.
8. Nash K, Sullivan J. Myoclonic seizures and infantile spasms. Pediatric Neurology. 2012;5:774-89.
9. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD001770. DOI: 10.1002/14651858.CD001770.pub3.
10. Shields WD. Infantile spasms: little seizures. BIG consequences. Epilepsy Curr 2006;6(3):63–69. doi:10.1111/j.1535-7511. 2006.00100.x
11. Glauser TA, Clark PO, Strawsburg R. A pilot study of topiramate in the treatment of infantile spasms. Epilepsia. 1998 ;39(12):1324-8.
12. Gibbs FA, Gibbs EL (1952) Atlas of Electroencephalography, 2nd ed.Addison-Wesley Press, Inc, Cambridge, Massachusetts. 222-224

13. Kellaway P,HracovyRA,Frost JD,Zion T.Precise characterization and quantification of infantile spasms.Ann Neurol.1979; 6: 214-218.9
14. Riikonen R. Long-term outcome of West Syndrome: a study of adults with a history of infantile spasms. Epilepsia 1996;37(4): 367–72.
15. Sadek AA, Mohamed MA, Meki ZF. Pattern and Outcome Of Infantile Spasms in Sohag University Hospital: A reterospective study. Sohag Medical Journal. 2018 Jul 1;22(2):135-42.
16. Panayiotopoulos CP (2011) A Clinical Guide to Epileptic Syndromes and their Treatment. 2nd edition. London: Springer
17. Fatema K, Rahman MM, Akhter S, Saad T, Akter N. Pattern of EEG Change in Infants with West Syndrome: A Retrospective Study. Epilepsy J. 2018;4(1000130):2472-0895.
18. O'Callaghan FJ, Edwards SW, Alber FD, Hancock E, Johnson AL, Kennedy CR, Likeman M, Lux AL, Mackay M, Mallick AA, Newton RW. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. The Lancet Neurology. 2017;16(1):33-42.
19. Riikonen R.Recent advances in the pharmacotherapy of infantile spasms.CNS drugs 2014;28:279-290.
20. Darke K, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Lux AL, Newton RW, O'Callaghan FJ, Verity CM, Osborne JP. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomised trial. Archives of disease in childhood. 2010 ;95(5):382-386.
21. Hrachovy RA,Frost JD-JR,Glaze DG.High-dose/long duration versus low-dose/short duration corticotrophin therapy for infantile spasms: a single blind study. J pediatrics 1994;124:803-806.
22. Riikonen R, Rener-Primec Z, Carmant L, Dorofeeva M, Hollody K, Szabo I, Krajnc BS, Wohlrab G, Sorri I. Does vigabatrin treatment for infantile spasms cause visual field defects? An international multicentre study. Developmental Medicine & Child Neurology. 2015;57(1):60-67.