Original Article

Seizures in patients with cerebral hemiatrophy: A prognostic evaluation

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Abstract

Purpose: Cerebral hemiatrophy is a common childhood disease. It clinically manifests with seizures, hemiparesis and mental retardation. **Materials and Methods:** In this prospective study, previously untreated patients with seizures and cerebral hemiatrophy were recruited. Cerebral hemiatrophy was diagnosed on the basis of hemispheric ratio. Patients with acquired hemiconvulsion, hemiplegia, and epilepsy (HHE) syndrome were included in group A. Group B included patients with congenital HHE syndrome. Patients were followed up for 6 months for seizure recurrence. **Results:** Out of 42 patients 26 were in group A and 16 were in group B. After 6 months, there was significant reduction in seizure frequency ($P < 0.0001$) in both the groups. At least 50% reduction in seizure frequency was noted in all the patients. Complete seizure freedom was observed in 15 (35.7%) patients. Seizure recurrences were significantly higher ($P = 0.008$) in group A. On univariate analysis, predictors of seizure recurrences were history of febrile seizures ($P = 0.013$), hippocampal sclerosis ($P = 0.001$), thalamic atrophy ($P = 0.001$), basal ganglia atrophy ($P = 0.001$), cerebellar atrophy ($P = 0.01$), ventricular dilatation ($P = 0.001$), epileptiform discharges at presentation ($P = 0.023$), complex partial seizures ($P = 0.006$) and status epilepticus ($P = 0.02$). On multivariate analysis, hemispheric ratio was the only significant factor for seizure recurrence. **Conclusion:** Patients with congenital hemiatrophy had better seizure control than that in patients with HHE syndrome.

Key Words

Cerebral hemiatrophy, childhood epilepsies, epilepsy, epilepsy syndrome, hemiconvulsion, hemiplegia, febrile seizures, seizure

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Introduction

Cerebral hemiatrophy, a disease of childhood, is characterised clinically by seizures, hemiparesis and mental retardation.[1,2] Dyke, Davidoff, and Masson, in 1933, described the plain skull radiographic and pneumoecephalographic changes, in a series of nine patients, characterized by hemiparesis, seizures, facial-asymmetry, and mental retardation.[3] Alpers and Dear recognized that this condition could be divided into congenital and acquired. A common etiology for congenital cerebral hemiatrophy is usually a large remote ischemic or hemorrhagic stroke during perinatal period. The secondary type often results from a cerebrovascular lesion, inflammatory process, or cranial trauma in early childhood.[1] Hemiconvulsion, hemiplegia, and epilepsy (HHE) syndrome is an important cause of acquired cerebral hemiatrophy.[4] HHE syndrome is diagnosed when cerebral hemiatrophy is associated with childhood febrile seizure or prolonged seizures and hemiparesis within seven days of seizure followed by delayed onset of partial seizure.[5] The exact mechanism of cerebral hemiatrophy is poorly understood. Two mechanisms have been proposed; vascular insult resulting in focal cerebral destruction and a prolonged childhood febrile seizures resulting in more diffuse or multifocal neuronal loss. The term cerebral hemiatrophy encompasses several etiological entities.[1,3,6-19]

Most of the information about cerebral hemiatrophy is available either in form of case reports or small case series. In this study, we aimed to prospectively evaluate the seizure pattern and 6 month seizure outcome in patients of cerebral hemiatrophy.

Materials and Methods

This prospective observational study, approved by the institutional ethics committee, was conducted in the Department of Neurology, King George's Medical University Lucknow, India from November 2010 to September 2013.

Informed consent was obtained from parents/guardians, before including the patient into the study.

In this study, we included previously untreated patients with seizures and possible cerebral hemiatrophy on visual evaluation of computed tomography. Cerebral hemiatrophy was, subsequently, confirmed on the basis of cerebral hemispheric ratio estimation. Hemispheric ratio was calculated by a method described by Bien and co-workers in patients with Rasmussen's encephalitis.[20] We used magnetic resonance (MR) images to calculate hemispheric ratio. In this method, cerebral MR imaging slice showing the Sylvian fissure and third ventricle was photographed. Sylvian fissure was taken as landmark, because perisylvian tissue is usually strongly affected by the atrophic process in patients with cerebral hemiatrophy (other than those caused by Rasmussen's encephalitis). Cerebral hemispheres were manually segmented into right and left halves, using image processing software, Adobe Photoshop CS3, Version 10.0 (Adobe Photoshop Inc., USA). Segmented halves were then turned into black color and measured in pixels with the help of software "Image J 1.45s'' (Wayne Rasband, National Institute of health, USA). Thresholding resulted in a "binary" image. Black pixels were the region of interests representing brain parenchyma; white pixels were background. Using the 'Analyze Particles' function, the size of each hemisphere (in pixels of the scanned picture) was determined. The ratio of the pixels of the affected and the unaffected hemisphere was computed. Values less than <1.0 were taken as criteria for cerebral hemiatrophy.[20,21] [Figure 1].

Detailed history from parents was taken with particular attention to prenatal, perinatal and postnatal events, developmental milestones, history of childhood febrile seizures, trauma, focal neurologic deficits and mental retardation. All available records were checked. On the basis of history provided by the parents and previous record available, patients were divided into two groups. Group A included patients of acquired HHE syndrome. This group included previously healthy child who were reported developmentally normal till they had a prolonged episode of seizures in the setting of fever.[5] Group B included patients with congenital cerebral hemiatrophy. Parents noticed disability immediately after birth. Patients with prolonged exposure to anti-epileptic drug, progressive hemiparesis with seizure, space occupying lesion on imaging, pregnant or lactating and inability to undergo magnetic resonance imaging (MRI) were excluded. We did not include patients with Rasmussen's encephalitis.

Seizure semiology was defined according to the International League Against Epilepsy classification.[22] Febrile seizure was defined as a seizure occurring in childhood between 1 month and 5 years of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure and not meeting criteria for other acute symptomatic seizures.[23-25] Hemiparesis was graded according to the motor item scale of the NIH Stroke Scale (NIHSS) for arm or leg (whatever was more paretic; 0 = no drift; 1 = limb drift; 2 = some effort against gravity; 3 = no effect against gravity; 4 = no movement). Disability was graded on modified Rankin Scale (MRS).[26,27]

Intelligence quotient was determined by experienced psychologists in all patients. MISIC (Indian adaptation of the Wechsler's Intelligence Scale for Children, Malin) was used between age-group 5-16 years.[28-30] This scale is used widely in testing the intelligence in children of age between 50-16 years. It provides a Full Scale intelligence quotient, a verbal intelligence quotient and a performance intelligence quotient. The reliability and validity of this instrument is well established. In the age group 3-5 years Seguin Form Board test was used.[29] Above 16 years "Wechsler Adult Intelligence Scale III" was used.[30] Categorization of Intelligence was done by intelligence quotient range contained in the DSM-IV-TR. The DSM-IV-TR lists types of mental retardation. Mild was defined as an intelligence quotient level of 50-70. Moderate if intelligence quotient level was 35-40 to 50-55. Severe between 20-25 to 35-40 and profound below 20-25 (http://behavenet. com/mental-retardation).

All enrolled patients were also subjected to electroencephalogram (EEG). Sixteen channel EEG was done with 10-20 international system of electrode placement (Clarity Brain Tech 40; Clarity Medical Private Limited, Mohali, India). The EEG was evaluated for presence of epileptiform discharges which included spikes, sharp, spike-wave or sharp wave complexes, voltage asymmetry, slowing of background activity and lateralization.

MRI brain was performed using Signa Excite 1.5 Tesla instrument (General Electric Medical Systems, Milwaukee,
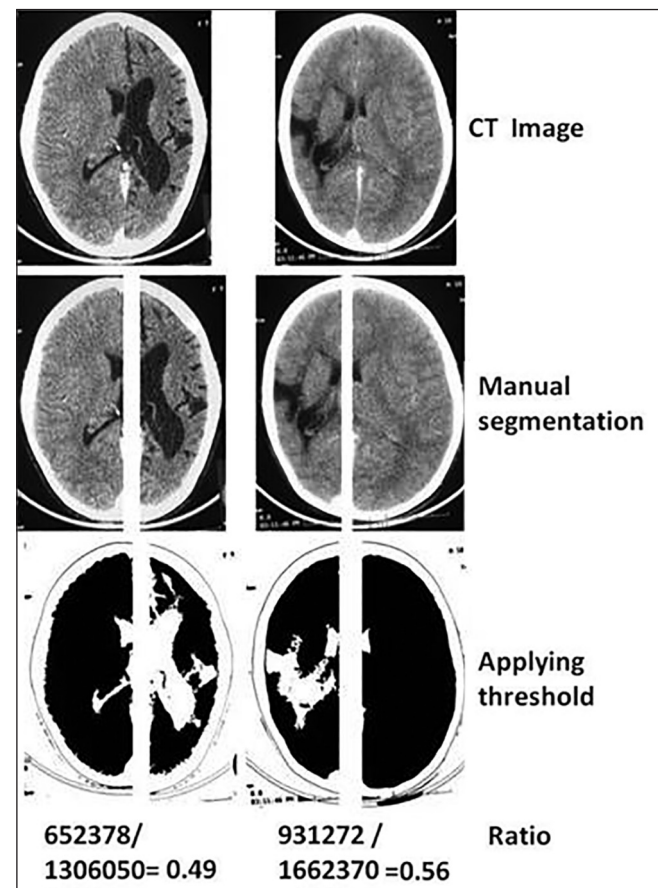

Figure 1: Calculation of hemispheric ratio as described by Bien and co-workers 20

WI, USA). The scans were reviewed by an experienced neuroradiologist, who was unaware of patient's clinical details. Each MRI was evaluated for the presence of focal signal intensity abnormalities in the cortex or white matter of the affected hemisphere, atrophy of the ipsilateral thalamus or contralateral cerebellum, compensatory calvarial changes of ipsilateral skull thickening and sinus overgrowth. Mesial temporal sclerosis were defined as abnormal morphology, volume loss, or abnormally increased signal intensity in the hippocampus on T2-weighted images and 3D spoiled-gradient recalled echo (SPGR) images.[31-34]

All the patients were given oxcarbazepine, at a dose according to their body weight. Oxcarbazepine (10 mg/kg) was given in 2 divided doses.[35-37] If a patient developed seizure recurrence, then the dose of oxcarbazepine was further increased (up to 20 mg/Kg, not exceeding 600 mg/day) or if seizures were not controlled with maximum oxcarbazepine dosage schedule, clobazam (5-10 mg per day) was added. Antiepileptic drug level

estimations were not performed. All patients were followed for 6 months. The seizure frequency, degree of hemiparesis and disability were assessed at each visit. Seizure controlled was defined as complete absence of seizure.[38] The factors associated with seizure control were analysed.

The statistical analysis was performed with the use of Statistical Package for Social Sciences, Version 16.0 for Windows (SPSS, Chicago, IL, USA) and Microsoft Excel. Univariate analysis was performed by Chi-square test for non-parametric data and student's t test for independent variables for parametric data and relative risks with 95% confidence interval (CI) were ascertained. For multivariate analysis, binary logistic regression was performed to see the impact of individual predictors of seizure control. Statistical significance was defined at a P value of <0.05 and wherever analysis was done it was two-tailed.

Results

Out of 48 patients that were recruited, three were excluded and three patients lost to follow-up. Finally, there were 26 patients were in group A and 16 patients in group B [Figure 2] The baseline characters of patients of both the groups have been shown in the Table 1.

Involvement of left cerebral hemisphere was insignificantly more frequent. Partial seizures with or without secondary generalization was the most frequent seizure types encountered in both the groups. Mean age of seizure onset was significantly lower in group B. There was no significant association between types of seizure and mean hemispheric ratio. Severe and profound mental retardation was found in group A only. Hemispheric ratio was significantly correlated with IQ ($P < 0.0001$). EEG was abnormal in 29 (69%) of the patients. Twenty-two patients had diffuse and multifocal abnormalities. In remaining seven patients the abnormalities were unilateral [Figure 3]. Most common MRI finding was ipsilateral ventricular dilatation, present in 59.5% ($n = 25$) of the patients. Other imaging abnormalities were focal cortical atrophy, hippocampal atrophy, white matter abnormalities, ipsilateral thalamic atrophy, ipsilateral basal ganglia atrophy, contralateral cerebellar atrophy and compensatory calvarial changes. History
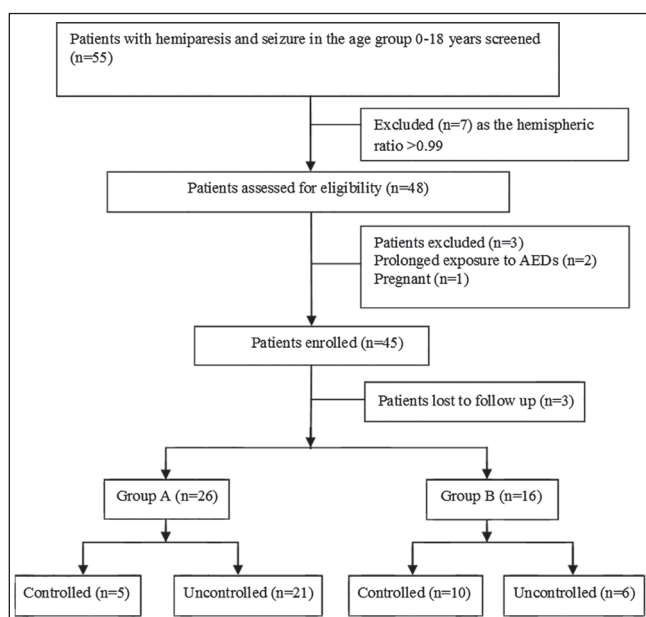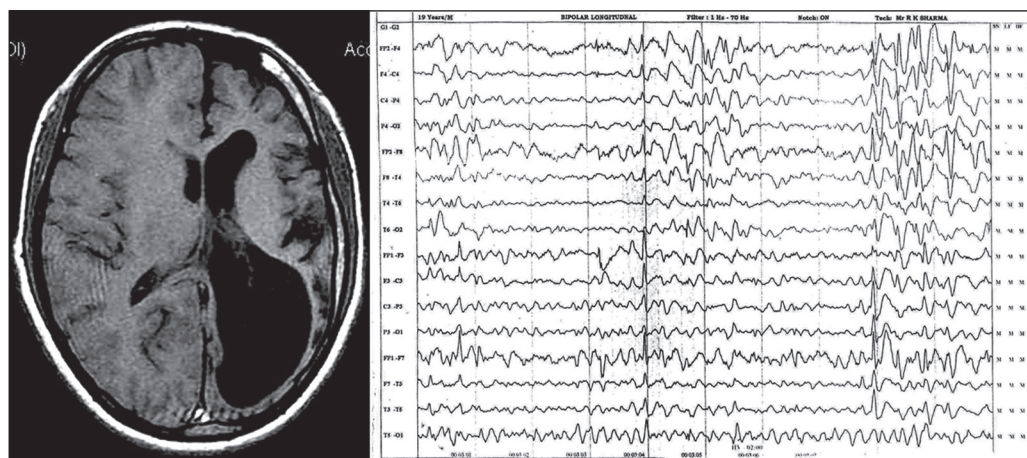

Figure 2: Flow diagram of the study

Figure 3: Electroencephalography showing focal and generalised epileptiform discharges in patient with right hemiatrophy

Table 1: Baseline characteristics of patients of epilepsy having cerebral hemiatrophy

Characteristics	Group A (n = 26) (%)	Group B (n = 16) (%)	Total (n = 42) (%)	χ^2	*P*-value
Demographic Profile					
Age (years; Mean + SD)	10.88±4.65	10.81±5.51	10.9±4.9	T = 0.045	0.964
Male: Female	15:11	9:7	24:18	0.008	1.000
Age at first seizure (Mean +SD; in years)	4.61±1.41	2.62±1.54	3.85±1.74	T = 4.274	<0.0001
Affected hemisphere (Left: Right)	15:11 (1.4)	9:7 (1.3)	24:18 (1.3)	0.008	1.000
Clinical Features					
Hemiparesis (NIH motor scale)					
0	–	–	–		
1	–	3 (18.8)	3 (7.1)	5.25	0.049
2	5 (19.2)	7 (43.7)	12 (28.6)	2.918	0.158
3	15 (57.7)	4 (25)	19 (45.24)	4.27	0.057
4	6 (23.1)	2 (12.5)	8 (9.5)	0.719	0.688
Disability (modified Rankin Scale)					
MRS 0	–	–	–		
MRS1	1 (3.9)	1 (6.3)	02 (4.8)	0.126	1.000
MRS2	3 (11.5)	1 (6.3)	04 (9.5)	0.321	1.000
MRS3	19 (73.1)	12 (75)	31 (73.8)	0.019	1.000
MRS4	3 (11.5)	2 (12.5)	05 (11.9)	0.009	1.000
Seizure type					
Partial motor	19 (73.1)	10 62.5)	29 (69.1)	0.518	0.510
Secondary generalized	13 (50)	8 (50)	21 (50.0)	0.000	1.000
Complex partial	13 (50)	2 (12.5)	15 (35.7)	6.067	0.020
Generalized tonic-clonic	1 (3.9)	1 (6.3)	2 (4.8)	0.126	1.000
Status epilepticus	13 (50)	3 (18.8)	16 (38.1)	4.102	0.056
Seizure frequency in last 2 month (preceding inclusion)	8	7	13	0.129	1.000
History of febrile seizures	26 (100)	4 (25)	30 (71.4)	27.3	0.0001
Category of Intelligence					
IQ (Mean + SD)	55.65±8.79	59.62±7.42	54.95±8.43	Z = −1.273	0.203
Borderline	0	1 (6.3)	1 (2.4)	1.665	0.381
Mild	21 (80.8)	13 (81.3)	34 (80.9)	0.001	1.000
Moderate	4 (15.4)	2 (12.5)	6 (14.3)	0.067	1.000
Severe	1 (3.9)	0	1 (2.4)	0.630	1.000
Imaging features					
Hemispheric ratio (Mean ± S.D)	0.82±0.15	0.86±0.10	0.84±0.14	T = −1.070	0.291
MRI					
Hippocampal sclerosis	16 (61.5)	0	16 (38.1)	15.905	<0.0001
Focal cortical abnormality	5 (19.2)	15 (93.8)	20 (47.6)	22.051	0.001
White matter abnormality	7 (26.92)	15 (93.75)	22 (52.38)	17.733	0.001
I/L Thalamic atrophy	19 (73.9)	2 (12.5)	21 (50.0)	14.538	0.001
I/L Basal ganglia atrophy	18 (69.2)	3 (18.7)	21 (50.0)	10.096	0.004
C/L Cerebellar atrophy	15 (57.7)	2 (12.5)	17 (40.5)	8.396	0.004
Compensatory calvarial changes	10 (38.46)	4 (25)	14 (33.33)	0.808	0.505
I/L ventricular enlargement	18 (69.2)	7 (43.7)	25 (59.5)	2.669	0.121
EEG					
Normal	6	7	13 (30.9)	1.981	0.187
Generalized and multifocal epileptiform discharges	17	5	22 (52.3)	4.627	0.055
Lateralized epileptiform discharges	3	4	7 (16.6)	1.292	0.397

Group A = Acquired HHE syndrome, Group B = Congenital HHE syndrome, EEG = electroencephalography, MRI = Magnetic resonance imaging, IQ = Intelligence quotient, I/L = Ipsilateral, C/L = Contralateral, MRS = Modified Rankin scale, NIH = National institutes of health

of febrile seizures were significantly ($P = 0.001$) correlated with hippocampal atrophy.

After 6 months, there was significant reduction in seizure frequency ($P < 0.0001$). At least 50% reduction in seizure frequency was noted in all the patients of both the group. Complete seizure freedom was observed in 15 (35.7%) patients, most of these patients belonged to group B. All patients, who were in seizure-free group, received only oxcarbazepine. Seizure recurrences were noted in 64.3%

(27) of patients. Clobazam was added in only in 10 patients of group A (seizure frequency not reduced with 600 mg oxcarbazepine). Addition of clobazam led to a 50% reduction in seizure frequency.

A significantly higher proportion of group A patients, in comparison to group B, continue to had seizure recurrences (81% versus 38%; $P = 0.008$). On univariate analysis the predictors of seizure recurrences were history of febrile seizures ($P = 0.013$), hemispheric ratio ($P = 0.01$), hippocampal sclerosis ($P = 0.001$), ipsilateral thalamic atrophy ($P = 0.001$), ipsilateral basal ganglia atrophy ($P = 0.001$), contralateral cerebellar atrophy ($P = 0.01$), ipsilateral ventricular dilatation ($P = 0.001$), epileptiform discharges at presentation ($P = 0.023$), complex partial seizures ($P = 0.006$) and status epilepticus ($P = 0.02$) [Figure 4]. On multivariate analysis, hemispheric ratio was the only significant factor associated with seizure recurrence.

Discussion

In present study, we evaluated the seizure pattern and seizure-related prognosis in patients with cerebral hemiatrophy. Cerebral hemiatrophy was categorized in two groups, congenital HHE syndrome and acquired HHE syndrome. All these patients of rural background did not receive medical attention. In all these patients antiepileptic treatment was started for the first time. Our study demonstrated that seizure frequency was significantly less following treatment with antiepileptic drugs, however, complete seizure freedom was observed only in 15 patients. Several clinical, electroencephalographic and neuroimaging features were associated with seizure recurrence. We observed that seizures were more difficult to control in patients with acquired HHE syndrome, in comparison to congenital HHE syndrome. Seizures, in patients with acquired HHE syndrome, are partial type originating from affected hemisphere. Seizures may also be partial with secondarily generalized type. In majority of the patients, seizures developed 1-3 years after the episode of febrile convulsions. Our findings suggested that seizures were

Figure 4: Kaplan Meier curve showing better seizure-related prognosis in patients with congenital hemiatrophy in comparison that in patients with acquired HHE syndrome

difficult to control in patients with extensive neuronal loss.[39-41] A major limitation to our study was a short follow up period, with an extended follow up a clearer seizure pattern would have emerged.

We in our study levelled symptomatic and idiopathic as acquired and congenital respectively. Originally, HHE syndrome was categorized in to two groups (symptomatic and idiopathic). Idiopathic HHE syndrome is only associated with fever and presumed extra-cranial infection while the symptomatic type is associated with fever as well as some identified, predisposing factor (head trauma, intracranial infection, or cerebral vascular disease).[39-42] However, Gastaut and co-workers, noted that this condition need to be distinguished from other infantile hemiplegia and epileptic conditions, occurring during the same age period, but resulting from perinatal (like obstetrical trauma) or antenatal pathology.[5] Criteria for idiopathic variety were presence of hyperthermia, absence of prolonged coma of neurological deficit except hemiplegia along with no evidence of any specific aetiology, variable neuroradiological sequelae (normal pneumoencephalogram, global ventricular dilatation, unilateral or segmental ventricular dilatation and no porencephaly or thrombosis) and presence of temporal lobe epilepsy of late-onset. In patients with symptomatic HHE syndrome epilepsy occurred earlier and was partial onset with secondary generalised type.[40] Possibly, frequently associated mesial temporal and hippocampal sclerosis results in refractory difficult to control epilepsy in patients with HHE syndrome.

HHE syndrome results after an episode of prolonged focal febrile convulsion in infancy and early childhood, with unilateral predominance. Neuroimaging studies have demonstrated unilateral oedematous swelling of the epileptic hemisphere at the time of initial status epilepticus. This acute phase subsequently results in cerebral hemiatrophy and appearance of epilepsy.[43] The exact mechanisms responsible for the development of HHE syndrome are not known. Some pathological studies have suggested that cytotoxic edema is responsible for neuronal damage. In patient with initial hemiconvulsion-hemiplegia syndrome, possible mechanisms that play a role in the development of later epilepsy include delayed cell death induced by cytotoxic edema and/or thalamic dysfunction causing a disruption of thalamo-cortical circuit.[43] A recent study analysed the characteristics of epilepsies as the sequelae of acute febrile encephalopathy with prolonged convulsions during childhood. Sixteen patients were retrospectively reviewed. These patients experienced febrile encephalopathy at the age of 11 months to 4 years. Five patients had unilateral lesions that manifested the phenotype of HHE syndrome. Epilepsy emerged with a latent period of 2 months to 2 years after the acute phase of febrile encephalopathy.[44]

In conclusion, patients with congenital hemiatrophy had better seizure control than that in patients with acquired HHE syndrome. More could be done, in these patients with difficult to control epilepsy, in optimizing medical therapy with anti-epileptic drugs with a longer follow up period.
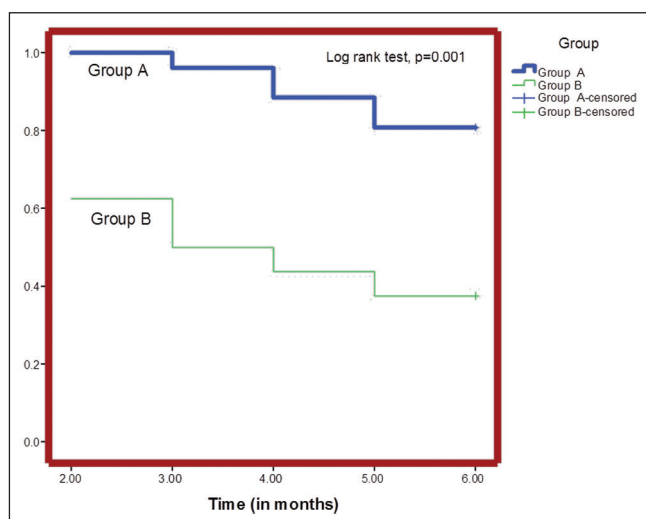
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