Original Article

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Morphometric Analysis of Corpus Callosum in Patients with Hypoxic Ischemic Encephalopathy (HIE)

Jain Avi Vinod[1], Jeevika M.V[2], Meghana S[1], Moinuddin Adil Mulla[1], Hita Shivayogi[1], Anusha BK[1]

[1]P.G. Junior Resident, JJM Medical College, Davanagere, Karnataka,[2]HOD, Department of Radiodiagnosis, JJM Medical College.

Abstract

Background: Corpus callosum (CC)- largest white matter structure in brain and has an important role in communicating both cerebral hemispheres. Damage to CC during development has been associated with poor neurological outcome, poor neuropsychological performance, cognitive and communication developmental delays. Aim and Objectives: Morphometric analysis of Corpus Callosum (CC) in HIE patients in comparison with CC of normal subjects by using MRI. **Subjects and Methods:** Retrospective comparative study of 40 patients-Ages < 2 year. Cases(20patients)-diagnosed cases of HIE on MRI. Controls (20patients)-proven to be normal on MRI. Two groups- ≤1 year and 1- 2 year age-group. Study was done on T1-mid-sagittal sections of brain obtained on PHILIPS-Achieva 1.5-Tesla-MRI. Statistical Data analysis of different measurements was done using't' test and 'p' values. **Results & Conclusion:** Variables were affected in order of Splenium>Body>Genu >Isthmus in ≤1year age-group and Genu>Splenium>Body>Isthmus in >1year age-group when mean value of different variables were compared between cases and controls. In HIE cases, thickest part was Genu and thinnest part was Isthmus. No statistically significant difference was found between males and females. This is one of the few studies providing biometric comparison between the CC of HIE patients and their controls. Damage to the CC during development is associated with poor neurological and neuropsychological performance, cognitive and communication developmental delays. This study analyzes the pattern of involvement of different variables of CC in HIE patients and helps in predicting the poor neurological outcome and developmental delays.

Keywords: Corpus Callosum, Hypoxic Ischemic Encephalopathy, Morphometric, MRI.

Corresponding Author: Dr. Jain Avi Vinod, PG Junior Resident, Department of Radiodiagnosis, JJM Medical College, Davanagere, Karnataka.

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Introduction

Corpus callosum (CC) is the largest white matter structure in the brain and has an important role in communicating the left and right cerebral hemispheres. Damage to the CC during development has been found to be associated with cognitive and communication developmental delays, vision impairment, lack of movement coordination, hearing problems, low muscle tone, distorted head or facial features, spasms, and seizures. Henceforth studying the morphometric changes in CC in patient with HIE by the use of MRI and comparing it with normal subjects will help in analyzing the damage to CC in HIE patients and thus helping in further management.

Objective:

Objective of the study is to do morphometric analysis of the CC in patients of HIE and comparing it with CC of the normal subjects by the use of MRI.

Subjects and Methods

Type of Study– Retrospective comparative study

Study Population

Retrospectively, 40 patients which were referred to the department of radiodiagnosis were included in the study out of which 20 patients which were diagnosed with HIE on MRI were taken as cases and other 20 which were proven to be normal on MRI were taken as controls.

Inclusion criteria:

For cases -

1. Age group less than 2 yrs old
2. Diagnosed HIE cases on MRI

For controls

1. Age group less than 2 yrs old
2. Diagnosed as Normal on MRI

Exclusion criteria:

For cases -

1. Age group more than 2 yrs old
2. Diagnosed with any disease/ disease process other than HIE.

For controls –

1. Age group more than 2 yrs old
2. Diagnosed with any disease/ disease process on MRI

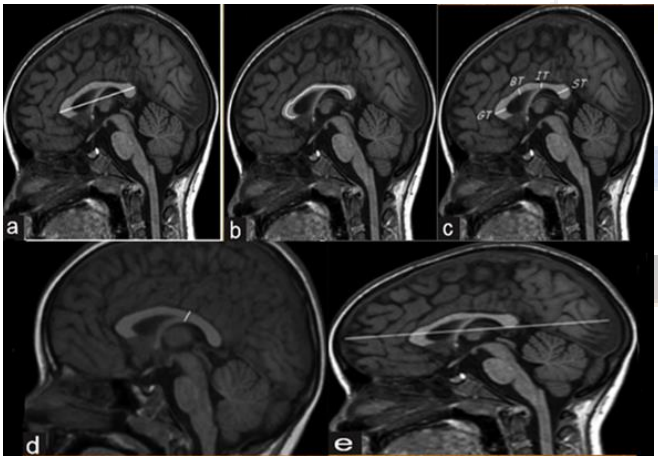
Imaging protocol:

MRI scanner PHILIPS Achieva 1.5 Tesla was used and study was carried out on T1 mid sagittal sections of the brain for morphometric analysis and diagnosis.

Methodology

Based on Garel et al. methodology, CC was calculated on mid- sagittal T1- weighted image by following methods:

a. Measurement of the anteroposterior diameter (APD) of the CC, the distance between the anterior aspect of the genu and the posterior aspect of the splenium
b. Measurement of the true length of CC (LCC), the curvilinear distance between the rostrum and the splenium at mid- thickness of the CC
c. Measurement of the thickness of the CC, at the level of the genu (GT), body (BT), isthmus (IT) and splenium (ST)
d. Measurement of the IT when the isthmus could not be identified because of insufficient CC modeling. IT was measured at the level where the fornix abuts the CC (CC- fornix junction)
e. Measurement of the fronto- occipital diameter (FOD), the distance between the between the extreme points of the frontal and occipal lobes



Statistical Analysis

The changes in corpus callosal morphometry were studied in HIE patients and compared with the controls and data analysis of different measurements was done using 't' test and 'p' values and outcomes were computed and compiled.

Results

Retrospective comparative study was carried and a total of 40 patients who fulfilled the selection criteria during the study were enrolled. The data were analyzed, and the final observations were tabulated as below.

In this study number participants were same in both the age groups in case and control group [Table 1 & Figure 1]. In this study, the maximum number of patients were in the age group of <1 year which were 70 % (n = 14) of total followed by age Group 1–2 years having 30% (n = 6) in this group as HIE is more common in less than 1 year age group. Same number of controls was taken for both groups (< 1 yr. and 1-2 yr. age group)

Table and Figure 1: Distribution of participants according to age.

Age	Group		Total
	Case	Control	
≤1 year	14	14	28
	70.0%	70.0%	70.0%
>1 year	6	6	12
	30.0%	30.0%	30.0%
Total	20	20	40
	100.0%	100.0%	100.0%

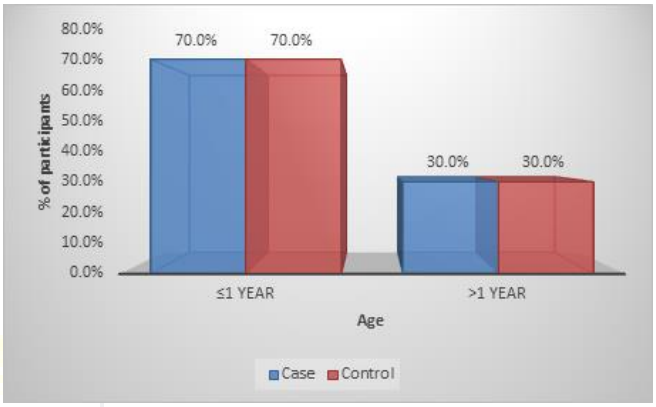
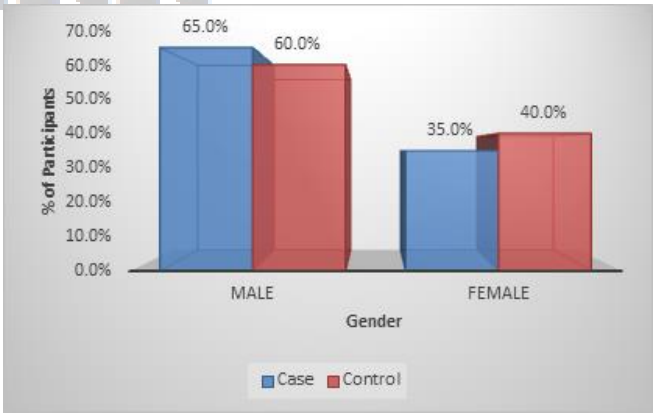


Table and Figure 2: Distribution of participants according to gender.

Sex	Group		Total
	Case	Control	
Male	13	12	25
	65.0%	60.0%	62.5%
Female	7	8	15
	35.0%	40.0%	37.5%
Total	20	20	40
	100.0%	100.0%	100.0%



In this study majority of patients were male in both the groups (65% in case group and 60% in control group) and female distribution was 35 % in case group and 40% in control group. Male predominance is due to the fact that HIE is more common in males [Table 2 and figure 2]

In the present study the mean of all the variable was more in control group compared to case group in ≤1 year age group. The result of independent sample t test reveals that in all the variables the mean difference is statistically significant between the groups (p value<0.05) [Table 3].

In cases < 1 year Dimensions of different parts of CC were in order of isthmus <body <splenium <genu. Thus, thickest part was genu (male - 5.10 mm, female - 4.4 mm) followed by splenium, and thinnest part is isthmus (male - 1.82 mm, female - 1.76 mm). Descending order of thinning was isthmus >body >splenium >genu. Thinning of isthmus was slightly more in female (mean width 1.76 mm) patients than male (mean width 1.82 mm).

But when mean value of different variables in cases were compared with the mean value of their respective variables in controls in age less than 1 year , the difference in mean value in both the groups was in order of Splenium > body > genu> isthmus. Thus splenium was was most affected variable when compared with control of the same age group.

We observed that in less than 1 year age group true length of corpus callosum (LCC) was more in both cases (4.56) and controls (6.06) as compared to APD of cases (3.89) and controls (4.88) respectively.

In the present study the mean value of all the variable was more in control group compared to case group in >1 year age group. The result of independent sample t test reveals that in all the variables the mean difference is statistically significant (p value<0.05) between the groups except FOD [Table 4].

In cases > 1 year Dimensions of different parts of CC were in order of isthmus <body <splenium <genu. Thus, thickest part was genu (male - 5.75 mm, female - 5.80 mm) followed by splenium, and thinnest part is isthmus (male - 2.40 mm, female - 2.35 mm). Descending order of thinning was isthmus >body >splenium >genu. Thinning of isthmus was slightly more in female (mean width 2.35 mm) patients than male (mean width 2.40mm)

But when mean value of different variables in cases were compared with the mean value of their respective variables in controls in age more than 1 year , the difference in mean value in of respective variables in both the groups was in order of Genu> splenium > body > isthmus .Thus Genu was the most affected variable when compared with control of this age group.

We observed that in more than 1 year age group true length of corpus callosum (LCC) was more in both cases(5.83) and controls(6.83) as compared to APD of cases (4.70) and controls (5.53) respectively.

In the present study in ≤1 year age group the mean value of variables GT, BT, IT and ST was more in male compared to female and remaining variables APD, LCC, FOD and APD/FOD ratio was more in female compared to male in case group. The result of independent sample t test reveals that none of the variables shown statistically significant difference between the male and female (p value>0.05) [Table 5].

Table 3: Comparison of case and control with respect to different variables in ≤1 year children.

Group		Mean	Std. Deviation	Std. Error Mean	t value	p value
APD	Case	3.89	0.57	0.15	-4.904	0.000
	Control	4.88	0.49	0.13		
LCC	Case	4.56	0.86	0.23	-5.005	0.000
	Control	6.06	0.72	0.19		
GT	Case	4.86	1.46	0.39	-3.153	0.004
	Control	6.45	1.18	0.32		
BT	Case	2.20	0.85	0.23	-5.746	0.000
	Control	3.91	0.72	0.19		
IT	Case	1.80	0.28	0.07	-8.129	0.000
	Control	3.24	0.60	0.16		
ST	Case	2.99	1.14	0.30	-5.160	0.000
	Control	5.39	1.32	0.35		
FOD	Case	10.75	0.88	0.23	-2.620	0.014
	Control	11.74	1.11	0.30		
APD/FOD	Case	0.36	0.05	0.01	-3.237	0.003
	Control	0.41	0.04	0.01		

Table 4: Comparison of case and control with respect to different variables in >1 year children.

Group		Mean	Std. Deviation	Std. Error Mean	t value	p value
APD	Case	4.70	0.18	0.07	-3.408	0.007
	Control	5.53	0.57	0.23		
LCC	Case	5.83	0.57	0.23	-2.448	0.034
	Control	6.83	0.82	0.34		
GT	Case	5.77	1.99	0.81	-2.503	0.031
	Control	8.25	1.40	0.57		
BT	Case	3.40	1.04	0.43	-2.390	0.038
	Control	4.73	0.88	0.36		
IT	Case	2.38	0.58	0.24	-4.674	0.001
	Control	3.67	0.34	0.14		
ST	Case	5.57	0.72	0.29	-2.722	0.021
	Control	7.15	1.23	0.50		
FOD	Case	12.38	0.92	0.37	-.568	0.582
	Control	12.73	1.20	0.49		
APD/FOD	Case	0.38	0.02	0.01	-5.149	0.000
	Control	0.43	0.02	0.01		

Table 5: Comparison of gender of children in ≤1 year age with respect to different variables in GROUP 1 (CASES)

Sex		Mean	Std. Deviation	Std. Error Mean	t value	p value
APD	Male	3.79	0.68	0.23	-0.916	0.378
	Female	4.08	0.23	0.10		
LCC	Male	4.48	1.04	0.35	-0.449	0.662
	Female	4.70	0.46	0.21		
GT	Male	5.10	1.73	0.58	0.797	0.441
	Female	4.44	0.80	0.36		
BT	Male	2.41	1.01	0.34	1.294	0.220
	Female	1.81	0.23	0.10		
IT	Male	1.82	0.32	0.11	0.385	0.707
	Female	1.76	0.21	0.09		
ST	Male	3.07	1.11	0.37	0.315	0.758
	Female	2.86	1.30	0.58		
FOD	Male	10.74	0.93	0.31	-0.030	0.976
	Female	10.76	0.89	0.40		
APD/FOD	Male	0.35	0.06	0.02	-1.090	0.297
	Female	0.38	0.02	0.01		

Table 6: Comparison Of Gender Of Children In ≤1 Year Age With Respect To Different Variables In GROUP 2 (CONTROLS)

Sex		Mean	Std. Deviation	Std. Error Mean	t value	p value
APD	Male	4.95	0.56	0.20	0.608	0.554
	Female	4.78	0.43	0.18		
LCC	Male	6.19	0.79	0.28	0.770	0.456
	Female	5.88	0.64	0.26		
GT	Male	6.34	1.37	0.48	-0.397	0.698
	Female	6.60	0.99	0.40		
BT	Male	3.96	0.87	0.31	0.323	0.752
	Female	3.83	0.50	0.20		
IT	Male	3.11	0.75	0.27	-0.930	0.370
	Female	3.42	0.30	0.12		
ST	Male	5.45	1.48	0.52	0.180	0.860
	Female	5.32	1.20	0.49		
FOD	Male	11.79	0.94	0.33	0.167	0.870
	Female	11.68	1.41	0.57		
APD/FOD	Male	0.41	0.03	0.01	0.276	0.787
	Female	0.41	0.04	0.02		

In the present study in ≤1 year age group the mean value of variables APD, LCC, BT, ST and FOD was more in male compared to female and in remaining variables GT and IT was more in female compared to male in control group. The result of independent sample t test reveals that none of the variables shown statistically significant difference between the male and female (p value>0.05) [Table 6].

Similarly Comparison of Gender of Children in >1 Year Age With Respect to Different Variables in Group 1. (Cases) And Group 2 (Controls) Was Done.

In the present study in >1 year age group the mean value of variables APD, IT and FOD was more in male compared to female and in remaining variables LCC, GT, BT, ST and APD/FOD ratio was more in female compared to male in Case group. The result of independent sample t test reveals that none of the variables shown statistically significant difference between the male and female (p value>0.05)

In the present study in >1 year age group the mean value in all the variables was more in female compared to male in Control group. The result of independent sample t test reveals that none of the variables shown statistically significant difference between the male and female (p value>0.05).

In our study, most of the CC dimensions did not differ much between male and female patients and none of the variables showed statistically significant difference between the male and female (p value>0.05).

Comparison of Age Groups of Children with Respect To Different Variables in Group 1 (Cases) and Group 2 (Controls)

In the present study the mean value of all the variable was more in > 1 year age group compared to ≤1 year age group in CASE group. The result of independent sample t test reveals that in all the variables the mean difference is statistically significant (p value<0.05) between the age groups except GT and APD/FOD ratio.

In the present study the mean value of all the variable was more in > 1year age group compared to ≤1 year age group in CONTROL group. The result of independent sample t test reveals that in all the variables the mean difference is statistically significant (p value<0.05) between the age groups except IT, FOD and APD/FOD ratio.

Discussion

HIE is one of the major causes of mortality and morbidity in neonates. Brain hypoxia and ischemia due to systemic hypoxemia, reduced CBF, or both are the primary physiological processes that lead to HIE.[1- 3] Neonatal HIE occurs in one to six per 1000 live full- term births. Of affected newborns, 15%–20% of affected newborns will die in the postnatal period, and an additional 25% will sustain

childhood disabilities.[4,5] Acute profound HIE tends to produce selective injury to the parts of the brain with the highest metabolic demands reflected by ongoing myelination. This leads to typical pattern of injury seen on MRI. Accurate identification and characterization of the severity, extent, and location of brain injury rely on the selection of appropriate neuroimaging modalities, including US, CT, and MRI. Conventionally, US used to be the first- line imaging technique for the evaluation of the newborn brain. In the present times,

MRI has become the state of the art imaging modality. Newer diagnostic techniques such as diffusion- weighted MRI and MR spectroscopy provide further insight into HIE and the potential for possible therapeutic intervention.

Studies of patients with agenesis of the CC or commissurotomy have demonstrated that the CC plays an important role in establishing hemispheric lateralization of function.[12] The significance of this structure which is the primary white matter commissure of the brain lies in the fact that damage to the CC during development has been found to be associated with poor neurological outcome and neuropsychological performance. In quite, a few studies, there has been established the direct quantitative correlation between thickness of the CC and volume of cerebral white matter in children with CP and developmental delay. The data of biometry of CC in HIE patients are scarcely available. Hence, this study is an effort toward drawing a conclusion about the growth pattern of CC in such patients. Retrospectively, 40 patients were included in the study out of which 20 patients which were diagnosed with HIE on MRI were taken as cases and other 20 which were proven to be normal on MRI were taken as controls. Morphometric analysis of the corpus callosal dimensions of the patients was made on mid- sagittal T1- weighted images at the level of cerebral aqueduct in hospital's PACS. All the MRI scans were done using PHILIPS Achieva 1.5-Tesla MRI using the head coils. In the present study, majority of patients were male in both the groups (65% in case group and 60% in control group) and female distribution was 35 % in case group and 40% in control group. Male predominance is due to the fact that HIE is more common in males. We included the patients up to the age of 2 years in the present study.

The maximum numbers of patients were under 1 year of age. This can be attributed to the fact that encephalopathy due to hypoxic- ischemic injury usually manifests within the first few hours after birth. In addition as suggested in the previous studies that despite improvements in perinatal care, asphyxia remains a major cause of mortality, resulting in up to 25% of perinatal mortality and morbidity and giving rise to between 8 and 15% of all cases of CP.

As the literature says, the CC originates at 10–11 weeks gestation and first develops rostrally to form the genu. Other parts of the CC, the rostrum (continuous below with the genu) and the splenium are formed after the trunk is developed, and by 16 weeks, the shape of the adult CC is recognizable.[14] In its early development, the genu grows faster than the splenium which does not show a rapid growth until after birth.[15] Thus, the later development of the splenium and posterior area of the CC make them particularly susceptible to damage in the third trimester and perinatal period.

Corpus callosum

The CC is a cerebral structure that reflects cognitive status in several neurological pathologies. Visual inspection of MRI has shown that HIE causes callosal damage. Periventricular leukomalacia caused by hypoxia- ischemia damage the periventricular crossroads of commissural, projection, and associative pathways, which are in a close topographical relationship with the lateral ventricles. MRI has facilitated diagnostic assessment of the CC. We tried in our study to explore to what extent HIE leads to changes in size of the CC.

Distances measured between different landmarks identified on the CC have also been evaluated.

In cases < 1 year were in order of isthmus <body <splenium <genu. Thus, thickest part was genu (male 5.10 mm, female 4.4 mm) and thinnest part is isthmus (male 1.82 mm, female 1.76 mm). In cases > 1 year Dimensions were in order of isthmus <body <splenium <genu. Thus, thickest part was genu (male 5.75 mm, female 5.80 mm) and thinnest part is isthmus (male 2.40 mm, female 2.35 mm. We observed that in both less than 1 year and more than 1 year age group true length of corpus callosum (LCC) was more in both cases and controls as compared to APD of cases and controls respectively.

In the present study we have compared the mean value of different variables of corpus callosum between cases and controls which was not done in any of the previous study.

Variables were affected in order of Splenium >Body>Genu >Isthmus in ≤1year age-group when mean value of different variables were compared between cases and controls.

Variables were affected in order of Genu>Splenium >Body>Isthmus in >1year age-group when mean value of different variables were compared between cases and controls.

Conclusion

To conclude our study data demonstrate that besides various established HIE manifestations corpus callosum is yet another important structure to be studied. Our study is one of the few studies providing biometric comparison between the CC of HIE patients and their controls. Most common site of injury was posterior part including isthmus and body where thinning secondary to loss of commissural fibers was found which is correlating with the growth pattern explained in literature and positively correlating with most vulnerable part getting damaged during perinatal periods of stress. However we have compared the mean value of different variables of corpus callosum between cases and controls which was not done in any of the previous study and we observed that Splenium was most affected variable when compared with control in ≤1year age-group and Genu was most affected variable when compared with control in >1year age-group .There was no sex effect observed in the size or morphology of the CC. Magnetic resonance imaging is valuable non-invasive, radiation free

tool with multiplanar capabilities which not only provides precise information regarding morphometry of corpus callosum but is also helpful in identifying the exact extent and site of the injury and other associated findings . Damage to the CC during development is associated with poor neurological outcome, poor neuropsychological performance, cognitive and communication developmental delays. this study analyzes the pattern of involvement of different variables of CC in HIE patients and helps in predicting the poor neurological outcome and developmental delays.

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