

MORPHOMETRIC ASSESSMENT OF HUMAN CORPUS CALLOSUM AND ITS CORRELATION WITH AGE AND GENDER- A MRI STUDY

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ABSTRACT

BACKGROUND

The Corpus Callosum (CC) has been a topic of controversy with regards to the subject of sexual dimorphism. Findings regarding age-related changes are also not same in various studies conducted. Most of the studies have been done on western population with very few on Indian subjects. This MRI study was carried out in South Asian population of Kerala origin with a large sample size of 300 people.

The aim of the study is to measure and analyse the age and gender-related differences in the size of human CC with MR imaging of brain.

MATERIALS AND METHODS

This observational study was done with a sample of 300 normal subjects who underwent MRI scan at the Department of Radiodiagnosis, Government Medical College, Alappuzha. Data was segregated on gender and age basis and various morphometric parameters of CC were statistically analysed using SPSS version 16.

RESULTS

It was observed that length of CC increased throughout life. Thickness of genu and body were observed to increase up to 45 years, whereas thickness of splenium increased up to 55 years with a decline thereafter. No significant gender differences were found in most of the parameters analysed.

CONCLUSION

Although, the study consisted of a larger sample, no key sex differences were observed in CC in most of the parameters studied. This suggests that the gender-related differences in connectivity may not be due to gender differences in morphology of CC. Age-related thinning was observed in anterior part of CC, a decade earlier than its posterior part.

KEYWORDS

Corpus Callosum, Gender Differences, Morphology, Connectivity, MRI, Splenium, Sexual Dimorphism, Age.

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BACKGROUND

The Corpus Callosum (CC) has always been the epicentre of a lot of debate and research following a report published by de Lacoste-Utamsing and Holloway¹ that claimed females to have a significantly larger splenium area. Since then, numerous studies have been conducted to study the age and gender changes seen in the CC. Several studies have found significant sex differences in length, shape and volume of CC with females having larger relative splenial width. On the contrary, there are studies, which nullify such gender differences. Conclusions regarding age changes in the CC have also not been reliable among the various studies done. The word Corpus Callosum (CC) in Latin means "a body, which is tough." It is a structure present in advanced mammalian brain in the depth of longitudinal fissure. It is the largest commissure of white matter seen in the human brain and is

made up of more than 200 million contralateral axonal projections. The CC is the main connector that is responsible for interhemispheric communications. It is about 10 cm long and consists of body, rostrum, genu and splenium. Splenium is the thickened posterior end of CC and lies about 6 cms in front of occipital pole. Genu is most anteriorly projecting part and lies about 4 cms behind the frontal pole in between the two lies the body of CC. The rostrum is the narrowest part that projects posteriorly from the genu.²

MR imaging allows study of CC in greater detail^{3,4} and with improved accuracy. Several imaging studies have shown the mid sagittal area of CC to show differences in morphology in relation to gender, handedness, ageing and pathological conditions.^{4,5} The CC has been shown to be affected in conditions such as schizophrenia, Alzheimer's and dyslexia even when the MR images reveal normal findings. Hence, measurements of CC have been proposed as useful pointers of disease progression.^{6,7,8,9,10} Very few studies have been performed in Indian population.^{11,12,13} The present study has been conducted using MRI scans to get a comprehensive data and to find out gender and age-related differences of CC in the population of Kerala.

MATERIALS AND METHODS

1. The sample for this observational study included the patients who were subjected to magnetic resonance

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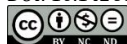
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imaging at the department of Radiodiagnosis at Government T.D. Medical College, Alappuzha. A total of 300 patients were selected for the study. Patients included were those with anatomically normal brain who underwent MRI for clinical conditions not known to cause any changes in the normal dimensions of CC like headaches, dizziness, hearing loss, infarcts, e.t.c.

- The patients were studied using MRI in mid sagittal plane by using a 1.5 Tesla machine of GE Company from January 2012-July 2013. The patients belonged to both sexes of different age groups ranging from birth to 85 years.

The MRI scans of 300 subjects (148 males and 152 females) were studied. The data was collected in a standard proforma. Name, age, gender and address of patients were noted and the measurements were recorded in millimetres. The scan film showing mid-sagittal section of brain passing through the CC was chosen for measurement. The following measurements were taken.

Measurements

Length of CC (LCC)- An anterior most point and a posterior most point were taken on the CC. The distance between the two was measured as length of CC.

- Distance between anterior point and frontal lobe (AF) - From the anterior most point, a horizontal line was drawn towards the maximum convexity of frontal lobe (Figure 1).
- Distance between posterior point and occipital lobe (PO)- From the posterior most point, a straight line was drawn towards the maximum convexity of occipital lobe (Figure 1).
- Length of the Brain (LB)- The distance was taken between the points F and O (Figure 1).
- AS- The shortest distance between anterior most point and the superior border of frontal lobe was measured (Figure 1).
- PS- Similarly, the shortest distance between posterior most point and superior border of occipital lobe was measured (Figure 1).
- Maximum thickness of genu, rostrum and splenium was measured (Tg, Tr, Ts) (Figure 2).
- Maximum Thickness of Body (Tb) was taken at its midpoint (M), which was taken at the centre of the length of CC (Figure 2).

Ratios

- Length of CC/length of brain - LCC/LB.
- Thickness of body at midpoint/length of CC - Tb/LCC.
- Maximum splenial thickness/length of CC - Ts/LCC.
- Maximum splenial thickness/length of brain - Ts/LB.

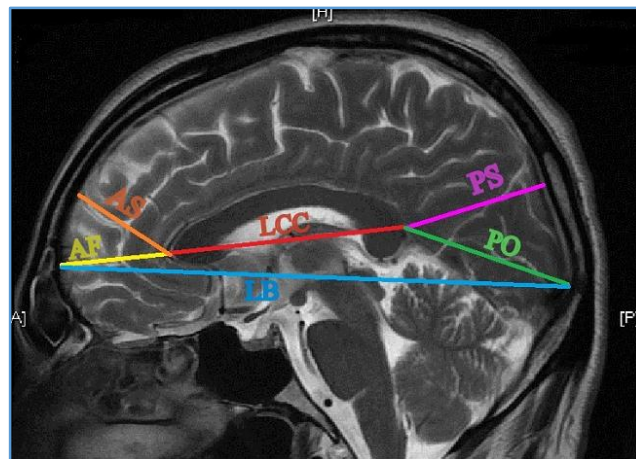


Figure 1. Mid Sagittal Section of Human Brain

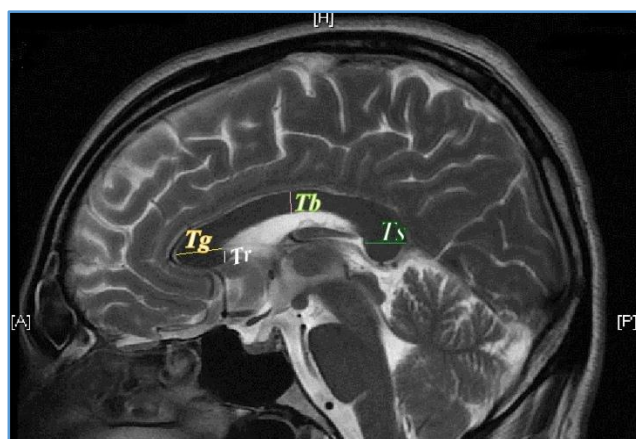


Figure 2. Mid Sagittal Section of Human Brain

All these dimensions were measured 3 times and an average value was taken. The measurements were taken using a marker calliper, which is software available in the computer. All these values were measured by a single observer. Finally, these measurements were correlated with age and gender. All these values were fed to the computer for detailed statistical analysis.

Statistical Analysis

The data obtained was entered in master charts. The range, arithmetic mean and standard deviation were calculated for quantitative data. To test the statistical significance of difference in the arithmetic mean between the male and female groups, independent sample t-test was used and Analysis of Variance (ANOVA) was done to assess the statistical significance of the difference in means among different age groups as it involved more than two groups. Statistical analysis was done using statistical software SPSS version.

RESULTS

	Age	N	Mean	SD	F	p value
Tb	<5	25	4.41	0.96	8.649	0.001
	5-9	25	5.27	0.74		
	10-14	29	5.49	1.00		
	15-24	36	5.46	0.79		
	25-34	42	6.02	1.06		
	35-44	45	6.02	0.84		
	45-54	48	5.62	1.13		

	55-64	28	5.37	1.23		
	>65	22	4.78	0.99		
	Total	300	5.49	1.08		

Table 1. Comparison of Mean Tb Among the Various Age Groups

	Age	N	Mean	SD	F	p value
Tg	<5	25	9.29	2.65	7.807	0.001
	5-9	25	11.19	1.67		
	10-14	29	11.37	1.71		
	15-24	36	11.36	1.47		
	25-34	42	12.10	1.81		
	35-44	45	12.22	1.66		
	45-54	48	11.65	1.56		
	55-64	28	11.48	2.07		
	>65	22	9.99	2.20		
	Total	300	11.36	2.00		

Table 2. Comparison of Mean Tg Among Various Age Groups

	Age	N	Mean	SD	F	p value
Ts	<5	25	7.88	2.47	9.772	0.001
	5-9	25	10.00	1.96		
	10-14	29	10.37	1.32		
	15-24	36	10.81	1.87		
	25-34	42	11.20	1.76		
	35-44	45	11.21	1.83		
	45-54	48	11.45	1.83		
	55-64	28	11.19	2.01		
	>65	22	10.20	1.89		
	Total	300	10.66	2.09		

Table 3. Comparison of Mean Ts Among Various Age Groups

LCC						
Age	Sex	N	Mean	SD	T	P
<5	Male	16	56.8	5.0	1.530	0.140
	Female	9	52.7	8.6		
5-9	Male	15	64.8	3.9	0.944	0.355
	Female	10	63.4	3.2		
10-14	Male	20	66.4	5.2	-0.562	0.579
	Female	9	67.4	2.0		
15-24	Male	12	67.4	3.6	0.352	0.727
	Female	24	66.9	3.8		
25-34	Male	19	70.0	3.9	0.722	0.475
	Female	23	69.1	3.8		
35-44	Male	20	74.1	4.1	3.107	0.003
	Female	25	69.9	4.8		
45-54	Male	23	71.2	4.8	1.250	0.218
	Female	25	69.7	3.5		
55-64	Male	16	72.5	5.4	0.730	0.472
	Female	12	71.2	3.6		
>65	Male	7	72.6	4.4	0.315	0.756
	Female	15	72.1	3.4		

Table 4. Comparison of Mean LCC Among Various Age Groups in Males and Females

AS						
Age	Sex	N	Mean	SD	t	p
<5	Male	16	38.0	5.1	3.686	0.001
	Female	9	29.2	6.8		
5-9	Male	15	36.0	2.7	1.253	0.223
	Female	10	34.5	3.2		
10-14	Male	20	37.8	3.1	1.411	0.170
	Female	9	36.0	3.3		
15-24	Male	12	34.2	3.7	0.486	0.630
	Female	24	33.5	4.1		
25-34	Male	19	34.4	3.4	1.246	0.220
	Female	23	33.0	3.5		

35-44	Male	20	34.9	2.6	2.057	0.046
	Female	25	33.1	3.0		
45-54	Male	23	33.5	3.6	1.224	0.227
	Female	25	32.3	3.2		
55-64	Male	16	35.0	2.2	4.918	0.001
	Female	12	31.5	1.4		
>65	Male	7	34.6	2.3	0.793	0.437
	Female	15	33.8	2.4		

Table 5. Comparison of Mean AS Among Various Age Groups in Both the Sexes

PS						
Age	Sex	N	Mean	SD	t	p
<5	Male	16	48.2	6.0	2.794	0.010
	Female	9	40.2	8.2		
5-9	Male	15	48.0	4.9	0.401	0.692
	Female	10	47.3	2.5		
10-14	Male	20	48.9	3.6	0.048	0.962
	Female	9	48.8	2.4		
15-24	Male	12	48.0	3.4	1.546	0.131
	Female	24	45.9	4.1		
25-34	Male	19	47.7	3.4	0.994	0.326
	Female	23	46.6	3.3		
35-44	Male	20	47.8	4.1	2.135	0.038
	Female	25	45.6	2.8		
45-54	Male	23	47.9	3.1	3.407	0.001
	Female	25	44.4	3.9		
55-64	Male	16	47.7	2.7	5.158	0.001
	Female	12	42.9	2.0		
>65	Male	7	45.7	2.4	1.369	0.186
	Female	15	43.9	3.1		

Table 6. Comparison of PS Across Age Groups in Both the Sexes

LB						
Age	Sex	N	Mean	SD	t	p
<5	Male	16	146.4	10.9	2.877	0.009
	Female	9	125.1	26.3		
5-9	Male	15	154.5	6.5	1.531	0.139
	Female	10	150.9	4.7		
10-14	Male	20	157.4	7.3	-0.552	0.585
	Female	9	158.9	5.7		
15-24	Male	12	156.0	5.7	1.232	0.226
	Female	24	147.8	22.5		
25-34	Male	19	159.0	8.3	2.008	0.051
	Female	23	154.6	5.8		
35-44	Male	20	162.6	8.1	4.229	0.001
	Female	25	153.8	5.9		
45-54	Male	23	158.7	7.1	3.232	0.002
	Female	25	152.5	6.3		
55-64	Male	16	161.5	9.2	3.380	0.002
	Female	12	150.8	6.9		
>65	Male	7	159.7	4.1	2.901	0.009
	Female	15	153.4	5.0		

Table 7. Comparison of Mean of LB Among the Various Age Groups in Both the Sexes

Observations

In this study, the following parameters of CC showed age changes-

- The length of CC was found to increase with advancing age. Mean LCC in less than 5 years is 55.36 ± 6.66 mm, which increased gradually to 72.23 ± 3.67 mm in more than 65 years.
- The thickness of body and genu were found to increase up to 45 years with a slight decline thereafter. The Tb

increased from young age (less than 5 years), peaked between 25-45 years (6.02 ± 0.84) mm and thereafter gradually decreased with age. The mean value of Tg increased up to 45 years (12.22 ± 1.66) mm thereafter declines with age.

- The thickness of splenium was found to increase up to 55 years after which there was a slight decline with age. Difference in mean Ts increased with age up to 55 years (11.9 ± 2.01) mm after which it started declining with age (greater than 65 years, 10.2 ± 1.89) mm.
- The AS (37.23 ± 3.20) mm and PS (mean = 48.86 ± 3.23) mm increased up to 15 years after which the value decreased with age. The minimum value of AS is mean of (32.06 ± 2.32) mm and PS is (44.46 ± 3.00) mm in the age group >65 years.
- The FA increases up to 15 years (mean = 39.71 ± 2.44) mm with a decline with age thereafter. Mean value in >65 years is 35.68 ± 2.37 mm.
- The LB increases up to 15 years (157.9 ± 6.8) mm after which the values remain unchanged. From 15 years onwards, no specific trend is seen. The mean values being variable. The mean value is minimum for the age group 15-25 years (150.5 ± 19.0).
- The ratio of LCC/LB increases up to 25 years after which the values are variable. It increases up to 25 years of age (mean = 0.4629 ± 0.15) mm beyond, which the values do not show a specific trend. The minimum mean value is seen in the age group of <5 years with mean of 0.4027 ± 0.039 mm.
- The ratio of Tb/LCC increases up to 35 years (mean value of 0.0869 ± 0.0158) mm with a slight decline thereafter to 0.0659 ± 0.01246 mm >65 years.
- The ratio of Ts/LCC increases up to 55 years age (mean = 0.1628 ± 0.02531) mm with a slight decline thereafter. Mean value in >65 years is (0.1408 ± 0.02303) mm.
- The ratio of Ts/LB increases up to 25 years (0.0741 ± 0.02265) mm after which the values decline with age. The mean value in >65 years is 0.0656 ± 0.1203 mm.
- The following parameters showed gender differences.
- The length of CC is more in males of the age group 35-45 years (74.1 ± 4.1) mm. No gender difference is seen before and after this age group.
- The Tb is more in males in less than 5 years. No gender difference seen beyond this age group.
- No gender difference is seen in thickness of rostrum, genu and splenium.
- The mean AS, PS, AF, PO, LB is significant in males of less than 5 years.
- The mean AS is significant in males when compared to females in less than 5 years (38 ± 5.1) mm. Thereafter, significant difference was seen among the males as compared to females during 35-45 years (34.9 ± 2.6) mm and 55-65 years (35 ± 2.2) mm.
- The mean PS is significant in males when compared to females in less than 5 years (48.2 ± 6) mm. Thereafter, significant difference is seen among the males as compared to females till 35-65 years.
- The mean value of AF is significant in males as compared to females in less than 5 years (39.9 ± 5.7) mm. Thereafter, significant difference is seen among the sexes

with males having larger values during 35-45 years and 55-65 years (36.3 ± 2.3) mm.

- The mean PO is significant in males as compared to females in less than 5 years (55.2 ± 7.1) mm. Thereafter, significant sex differences are seen in males in the age group between 35-65 years and beyond.
- The mean LB is significant in males when compared to females in less than 5 years (146.4 ± 10.9) mm. Thereafter, significant difference is seen among the males as compared to females during 35-65 years and beyond.
- The ratio of LCC/LB is significant in females less than 5 years. It again becomes significant in females in the age group 55-65 years. The mean value is more in females as compared to males in less than 5 years (0.43 ± 0.05) mm. A significant difference is seen among the males and females with females showing larger values during 55-65 years (0.47 ± 0.02) mm.
- The ratio of Tb/LCC is significant in males of the age group less than 5 years. Thereafter, no difference is seen among the sexes. The ratio is significantly high in males in less than 5 years (0.08 ± 0.01) mm. Thereafter, no significant difference is seen among the sexes with ageing.
- The ratio of Ts/LCC and Ts/LB is not significant among the sexes.

DISCUSSION

A lot of debate is centred on the morphology of CC in relation to age and sex. The main objective of this study is to measure, analyse and estimate the age-related changes and gender-related differences in the population of Alappuzha. The baseline data thus obtained can be used by the neuroradiologists, neurologists, psychiatrists and basic medical scientists for research and clinical purposes.

Age-Related Changes in Morphology of CC

In our study, the absolute length of CC was found to increase with age, which was consistent with the findings of Suganthi J¹¹ et al and Takeda S¹⁴ et al. This maybe because with advancing age, a person is more and more exposed to a complex and enriched environment resulting in an increase in afferent synapsal connections¹⁵ that in turn may lead to increase in length of CC with age. However, the relative increase in CC length, which is LCC/LB was seen only up to 25 years.

The thickness of the body of CC [Tb] and the thickness of genu [Tg] was seen to increase up to 45 years after which there was a gradual decline with age. Similarly, the thickness of splenium [Ts] was found to increase up to 55 years after which a gradual decline with age was noted. Among the callosal ratios, Ts/LB, Tb/LCC and Ts/LCC were noted to increase with age up to 25, 35 and 55 years, respectively beyond which they decreased with age. This is in concordance with the findings of Lissette J¹⁶ who observed that older adults show age-related atrophy in the anterior and middle sections of the CC, the posterior part does not appear to be susceptible to age-related atrophy. Weis¹⁷ et al also noted that genu and width of anterior parts of CC decreased significantly with ageing suggesting alteration in frontal and temporal interhemispheric fibre. Studies addressing callosal and structural interhemispheric function suggest that the efficiency of the interhemispheric transfer of information decreases with increasing age and this maybe

one factor contributing to the wide range of cognitive, motor, visuoperceptual and communication-related difficulties experienced by ageing adults.¹⁸ This might be because of age-related cortical atrophy, especially in frontal lobes^{19,20} resulting in loss of cortical neurons, which in turn causes secondary loss of callosal fibers. As the anterior parts of CC carry axons from the frontal, premotor and motor cortices, this age-related atrophy though relatively small is more in the anterior parts of CC than in the posterior parts.

The value of AS, PS, AF and LB increases up to 15 years, which can be attributed to the growth of the brain during the initial growing years. After that, the values of AS, PS and AF start declining gradually, whereas the length of the brain does not change. This may be due to the fact that the LCC increases throughout the age, thereby resulting in a relative decrease in the distances of AS, PS and AF. This is in concordance with the Monro-Kellie doctrine, which states that the cranial box is rigid and constant in volume and contains brain, blood and cerebrospinal fluid. If anyone of the constituents increases, the other two must diminish. Later on, cortical atrophy set in resulting in gradual decline in these values. Studies have shown that the rates of global atrophy in healthy people increase gradually with age from an annual rate of 0.2% a year at age 30-50 to 0.3-0.5% at age 70-80.¹⁹

Gender-Related Differences

Many studies have shown sexual dimorphism in different parts of CC; however, none of them have demonstrated a consistent result. In this study, the mean LCC was more in men than women in all the age groups, but a statistically significant difference was seen only in the age group of 35-45 years ($p=0.003$). Gupta et al¹² and Suganthy et al¹¹ also noted men to have a longer CC among the Indian population. The gender difference may be attributed to the fact that men in their 30's and 40's are more active professionally as compared to their female counterparts, hence requiring increased recruitment and interhemispheric communication for efficient performance of the complex multiple tasks.

In our study, the mean Tb was more in males as compared to females in all groups, but a statistically significant difference was seen only in the age group of <5 years ($p=0.007$). This is contrary to the findings of Allen L. S et al²¹ who did not find any significant sex differences in the CC of children aged 2-16 years. This difference observed in the early childhood maybe due to effect of the perinatal gonadal hormones, which are responsible for the sexual dimorphism in the fetuses. The axonal pruning²² taking place later in the development may account for the lack of sex differences observed in other age groups. This was similar to the findings of Witelson²³ who found anterior parts of body of CC to be larger in males. No gender differences were observed in the Tg and Tr in our study.

Sexual Dimorphism in Splenium

Many studies have reported an increase in size of splenium in females. In this study, although the mean Ts was more in females than males, a statistically significant difference was not observed. This was similar to the findings of Takeda¹⁴ and Suganthy¹¹ et al who did their studies in Japanese and Indian populations, respectively. Our results do not correlate with the findings of Atif Aydenlioghi²⁴ et al, Davatzikos²⁵ et al and

Gupta T et al¹² who demonstrated a robust sex difference in the splenium of females.

The values of AS, PS, AF, PO and LB were significantly higher in males as compared to females ($p=0.001$). These were consistent with the findings of Gupta T et al.¹² On subgroup analysis, all these parameters showed a statistical significant difference in males in the age group of less than 5 years. Also, as the age advances, statistically significant difference was observed in AS among males of the age group of 35-45 years and 55-65 years. Likewise, the value of AF, PS, PO and LB was also statistically significant in males in the age group 35-65 years.

The sex differences seen in early childhood maybe due to the fact that nearly all the sexually dimorphic parameters in the brain including CC are influenced by perinatal gonadal hormone levels. The gonadal hormones during a critical period of perinatal development may influence the survival of neurons and the number of axons coursing through the CC of humans.²⁶ Probably, later in development, callosal axonal pruning²² may take place resulting in absence of any sex difference. The sex differences seen later in life maybe the result of a different ageing process that may occur in the brains of men than women mediated through hormonal^{27,28} and environmental factors.^{29,30}

Among the ratios, LCC/LB, Ts/LB were found to be statistically significant among the sexes with females showing higher values. Elster et al³¹ and Janacke³² et al also found the ratio of Ts/LB to be significantly high in females, which they attributed to the smaller size of their brain rather than the gender.

CONCLUSION

Thus, among the age-related changes, the anterior part of CC was found to be affected a decade earlier as compared to posterior part of CC. No gender-related differences were observed in most of the parameters studied. Though, our study is one that comprises a larger sample, we did not observe substantial sex differences in CC to propose that the gender-related differences in the hemispheric functions are due to gender differences in connectivity. This study provides analysed data to be used as reference for the neuroradiologists, neurologists, psychiatrists and neurobiologists for their clinical and research activities.

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