BRAIN INJURY, NOVEMBER 2003, VOL. 17, NO. 11, 1003–1009

Taylor & Francis
healthsciences

Corpus callosum atrophy in adolescents with antecedents of moderate perinatal asphyxia

CRISTINA MAÑERU†, CARME JUNQUÉ, PILAR SALGADO-PINEDA†, JOSEP M. SERRA-GRABULOSA†, DAVID BARTRÉS-FAZ†, BLANCA RAMIREZ-RUIZ†, NÚRIA BARGALLÓ‡, MERCÈ TALLADA§ and FRANCESC BOTET‡

† Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
‡ Hospital Clínic, Faculty of Medicine, University of Barcelona, IDIBAPS, Barcelona, Spain
§ Services of Neurophysiology and Neurology, Vall d'Hebron Children Hospital, Barcelona, Spain

(*Received 23 September 2002; accepted 3 March 2003*)

Background: The corpus callosum (CC) is a cerebral structure that reflects cognitive status in several neurological pathologies. Visual inspection of MRI has shown that hypoxic-ischemic encephalopathy (HIE) causes callosal damage.
Primary objective: To quantify the CC surface in a sample of patients with antecedents of HIE and a group of matched controls.
Research design: Comparisons of CC measures among control subjects, mild HIE patients and moderate HIE patients as well as correlates of CC surface and neuropsychological performance.
Methods: Twenty-one adolescent patients with childhood antecedents of HIE were compared to 21 controls. ANALYZE software was used to semi-automatically measure the CC area.
Main outcomes and results: Patients with moderate HIE showed corpus callosum reduction. The isthmus and genus were the most affected regions. Corpus callosum size correlated with cognitive function.
Conclusions: Corpus callosum quantification provides new evidence of subtle residual deficits in subjects with HIE antecedents without apparent neurological sequelae.

Introduction

Magnetic resonance imaging (MRI) studies have described several patterns of hypoxic-ischemic encephalopathy (HIE)-related cerebral lesions involving different cerebral structures such as the hippocampus and the basal ganglia, among others [1–6]. These patterns vary according to the type and duration of asphyxia. White matter lesions are often seen in both premature and at term infants, and are particularly associated with partial and prolonged asphyctic episodes [7, 8]. Myelinization delay, *ex vacuo* ventricular dilation and corpus callosum thinning

Correspondence to: Professor Carme Junqué, PhD, Departament de Psiquiatria i Psicobiologia Clínica, IDIBAPS, Universitat de Barcelona, Casanova 143, 08036 Barcelona, Spain. e-mail: cjunque@psi.ub.es

Brain Injury ISSN 0269–9052 print/ISSN 1362–301X online © 2003 Taylor & Francis Ltd
http://www.tandf.co.uk/journals
DOI: 10.1080/0269905031000110454

are the most common signs of white matter impairment observed in HIE patients [2–4].

Anatomical cerebral studies in adults who have survived hypoxia episodes have shown marked atrophy of the hippocampi and corpus callosum together with cerebral atrophy and ventricular enlargement [7–11]. Most neuroimaging studies of the brain correlates of HIE have been performed during the early stages of cerebral development [1–6, 9] and only a few investigations have been carried out in adults or adolescents with early history of HIE using quantitative measurements of cerebral regions [11–13].

The corpus callosum is a region that is especially vulnerable to brain damage, such as that caused by traumatic brain injury (TBI) [14]. In a previous study, it was found that, among adolescents who had suffered moderate-to-severe TBI in childhood, the corpus callosum area correlated strongly with several measures involving processing speed and visuospatial function [15]. Other reports of neurologically impaired patients and normal subjects also indicate that CC integrity is associated with clinical or cognitive status [10, 16–19]. Corpus callosum atrophy has been previously been reported in children suffering hypoxic-ischemic encephalopathy. However, most of these findings were based on visual inspections of brain images or were performed during the early stages of development. Visual inspection may be sufficient to identify consequences of severe HIE, but classical procedures of this kind may not be able to identify cerebral correlates of HIE in moderately or mildly affected patients. More precise analysis by means of semi-automated quantitative methods may be required.

The present study aimed to evaluate quantitative measures of corpus callosum as possible predictors of long-term neuropsychological sequel in adolescents who had suffered perinatal asphyxia.

Methods

Subjects

Twenty-one adolescents with antecedents of mild or moderate neonatal encephalopathy related to perinatal asphyxia were studied. The neuropsychological performance of 28 cases with these characteristics has been described in a recent paper by this group [13]. The present report studied the cases that agreed to undergo MRI examinations. The sample included six patients with mild HIE and 15 with moderate HIE. The control group consisted of 21 age, gender and laterality matched subjects (see table 1). All patients except one were right-handed.

Table 1. Demographic characteristics of patients and control subjects. Values are given in means (standard deviations)

	Patients		Control group ($n = 21$)
	Mild HIE ($n = 6$)	Moderate HIE ($n = 15$)	
Age	15 (2.45)	15.87 (3.14)	16.67 (2.87)
Years of formal education	9.17 (1.94)	10.07 (2.69)	11.05 (2.6)
Gender (% women)	83.3	33.3	47.6

MRI examinations

All MR scans were performed on a 1.5T Signa (General Electric, Milwaukee, WI). The protocol included axial T2Wdual FSE (4000TR/20-100TE/1nex/3 mm slice thick) and coronal 3D SPGR 300TR/min full TE/20 flipα/1nex /1 mm slice thick recon) field of view (FOV) 24×24 and matrix 256×256. MR images were analysed by means of ANALYZE 4 program (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN) installed in a SUN ultra 60 workstation (SUN Microsystems). The image analyses were carried out by two investigators who were blind to the subjects' clinical and neuropsychological characteristics.

The surface area of the corpus callosum (CC) was measured on mid-sagittal T1-weighted sections from the anterior-most part of the rostrum to the posterior-most part of the splenium, in accordance with a method described elsewhere [15, 16, 20]. The CC was defined as a region of interest (ROI) and was automatically delineated in its perimeter in the mid-sagittal section by means of the intensity threshold routine from the ANALYZE program. After a manual correction guided by visual inspection, the total CC area was calculated automatically. In a subsequent analysis, CC was partitioned into seven regions, as described in Witelson [21] (see figure 1). These CC sub-divisions are thought to reflect a general topographical organization of the CC in relation to distinct cortical regions. To control for inter-subject variability in brain size, all CC measures were adjusted to the intracranial area (ICA) using the following procedure: Corpus Callosum area/Intracranial area $\times$ 100 [20, 22]. The criterion used to determine the mid-sagittal plane was the one previously established by Giedd *et al.* [23]: presence of the cerebral aqueductum and of the septum pellucidum and visualization of the thalamus.

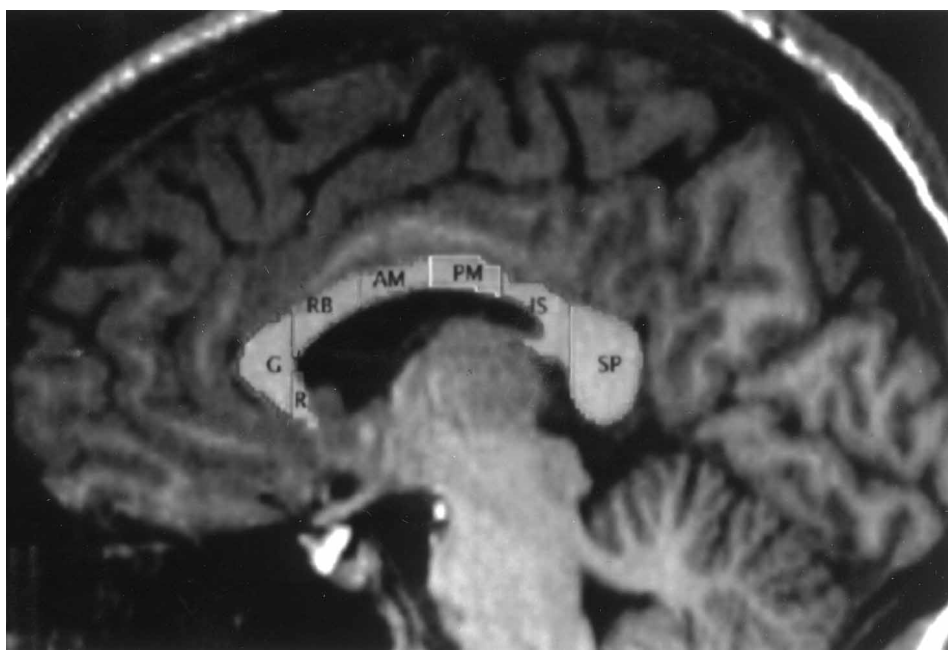

Figure 1. Corpus callosum sub-divisions (R: Rostrum; G: Genu; RB: Rostral Body; AM: Anterior mid-body; IS: Isthmus; SP: Splenium).

Neuropsychological assessment

Patients and control subjects were evaluated using tests of memory and frontal lobe function as described previously [13]. To avoid statistical problems deriving from multiple comparisons between cognitive and brain measures, three composite neuropsychological variables were obtained from the mean standardized (z) scores of patients and controls. A first cognitive variable was obtained reflecting the global cognitive functioning of subjects and patients in memory and frontal lobe tests. This measure was obtained using the following neuropsychological tests: Stroop test (interference condition), Digit Symbol Test (WISC-R), Rey Auditory Verbal Learning Test and Visual Reproduction (WMS-R). The variable was then divided in two further measures of 'frontal lobe' (mean z-scores of Stroop, Digit Symbol test) and 'memory function' (Rey Auditory Verbal Learning Test, Visual Reproduction).

Statistical analysis

Statistical comparisons were performed by means of the Statistical Package for the Social Sciences (SPSSWin, v. 9.0). One-way analysis of variance (ANOVA) with Scheffé multiple comparisons were used to examine the CC and neuropsychological values among groups. Pearson coefficient correlations were used to relate brain morphology with cognitive performance.

Results

MRI findings

Table 2 shows the absolute and corrected CC areas for each group. Comparisons among the three groups showed significant differences both for the uncorrected and ICA-adjusted CC measurements, but not for the ICA area alone. *Post-hoc* analyses from CC ICA-adjusted measures demonstrated that subjects with moderate HIE differed significantly from both controls ($p = 0.009$) and mild HIE individuals ($p = 0.011$). However, controls and mild HIE did not differ in CC measurements ($p = 0.376$).

Segmenting CC into different regions showed that the differences found between sub-groups of subjects were mainly attributable to increased atrophy in the isthmus region in the moderate HIE group (vs controls $p < 0.001$; vs mild HIE

Table 2. Descriptive values of corpus callosum and intracranial area. Values are expressed in mm^2 and given in means (standard deviations)

	Patients			
	Mild HIE ($n = 6$)	Moderate HIE ($n = 15$)	Control group ($n = 21$)	p
Corpus Callosum (CC)	732.72 (87.28)	605.16 (105.51)	722.42 (109.97)	0.005
Intracranial Area (ICA)	14 978.91 (1033.09)	14 974.22 (1059.85)	15 450.88 (1031.94)	0.34
CC/ICA ×100	4.91 (0.64)	4.03 (0.63)	4.66 (0.55)	0.003

p = Statistical significance from One-way Analysis of Variance; CC = Corpus Callosum; ICA = Intracranial area.

group $p < 0.026$), whereas no significant differences were found between controls and mild HIE ($p < 0.8$). The genus was also significantly atrophic in moderate HIE patients compared to controls ($p < 0.007$).

Neuropsychological performance

Control subjects performed better in all composite neuropsychological measures than moderate HIE individuals (global functioning: $p < 0.0001$; frontal lobe: $p < 0.003$; memory: $p < 0.01$) and had higher scores in memory functioning than mild HIE patients ($p < 0.047$). No significant differences were found between mild and moderate HIE patients (not shown).

MRI and cognitive relationships

Whole area measures of corpus callosum adjusted for mid-sagittal surface correlated positively with the composite measure of global cognitive functioning ($r = 0.34$, $p < 0.03$) and showed a trend towards statistical significance when correlated with the measure of frontal lobe functioning ($r = 0.29$, $p < 0.06$), but not with the measure of memory performance ($r = 0.13$, $p < 0.41$). When correlations between function and brain measures were studied within the different sub-regions of the CC, only the isthmus and the genus were associated with frontal lobe functioning (genus: $r = 0.38$, $p < 0.01$; isthmus: $r = 0.33$, $p < 0.03$), but not with memory performance (genus: $r = -0.6$, $p < 0.7$; isthmus: $r = 0.09$; $p < 0.56$).

Discussion

The corpus callosum was found to be smaller in adolescents with perinatal antecedents of moderate asphyxia than in a well-matched sample of healthy subjects. After segmenting the CC in several sub-regions, it was found that the atrophy was mainly observed in the genus and the isthmus areas.

Corpus callosum atrophy has been previously described in developmental disorders such as attentional deficit disorder with hyperactivity or dyslexia [17, 24–27]. However, previous studies of CC integrity in HIE patients have been limited to visual inspections or to examinations in pre-adolescent patients. The findings add further support to these studies, demonstrating that CC atrophy can be observed as a long-term sequel of HIE patients using quantitative MRI measurements.

The callosal atrophy found in HIE patients with antecedents of moderate perinatal asphyxia may be induced by indirect axonal damage as a consequence of diffuse neuronal loss secondary to the perinatal brain insult.

In these subjects, CC measurements correlated with neuropsychological performance. The association of CC integrity with cognitive status is in line with previous findings reported in other conditions [10, 16–19, 28]. The importance of the corpus callosum in cognitive functioning has been further emphasized in previous reports including patients with TBI or corticobasal degeneration, which stated that the degree of cognitive impairment showed a stronger correlation with the severity of corpus callosum atrophy than with other MRI measures such as cortical atrophy or ventricular enlargement [15, 18] .

Corpus callosum is a major anatomical and functional cerebral commissure linking associative areas of both hemispheres. When intact, it probably contributes

to a better neuropsychological performance [24]. The damage to the corpus callosum may have adverse developmental implications because these regions continue to mature through adulthood, possibly increasing in size due to myelinization [29]. A tendency towards a correlation between corpus callosum size and performance in frontal lobe tests was found. Frontal lobe functioning requires the maturity of white matter and functioning of posterior cortical regions [30]. Thus, a structure serving as an anatomical and functional link may play a key role in executing frontal lobe tests.

In summary, the findings of this study show that individuals with perinatal antecedents of moderate HIE present greater callosal atrophy than normal subjects. The atrophy affects mainly the genus and isthmus regions. Measurement of the callosum surface is straightforward and is able to detect subtle neuroanatomical sequel in subjects with HIE and good outcome.

Acknowledgements

This work was supported by the Grant PM 98-0192 from the Spanish Ministry of Education and Culture, and Grant 99SGR00081 from the Generalitat of Catalonia. Cristina Mañeru holds a Research Grant from the University of Barcelona. David Bartrés-Faz was funded by a Post-doctoral research grant from the Spanish Ministry of Education and Culture (MEC/FULLBRIGHT).

References

1. McArdle, C., Richardson, C., Hayden, C. *et al.*: Abnormalities of the neonatal brain: MR imaging. Part II: hypoxic ischemic brain injury. *Radiology*, **163**: 395–403, 1987.
2. Keeney, S. E., Adcock, E. W. and McArdle, C. B.: Prospective observations of 100 high-risk neonates by high-field (1.5 Tesla) magnetic resonance imaging of the central nervous system. II. Lesions associated with hypoxic-ischemic encephalopathy. *Pediatrics*, **87**: 431–438, 1991.
3. Barkovich, A. J. and Truwit, C.: Brain damage from perinatal asphyxia: correlation of MR findings with gestational age. *American Journal of Neuroradiology*, **11**: 1087–1096, 1990.
4. Steinlin, M., Dirr, R., Martin, E. *et al.*: MRI following severe perinatal asphyxia: preliminary experience. *Pediatric Neurology*, **7**: 164–170, 1991.
5. Barkovich, A. J.: MR and CT evaluation of profound neonatal and infantile asphyxia. *American Journal of Neuroradiology*, **13**: 959–972, 1992.
6. Barkovich, A. J. and Sargent, S. K.: Profound asphyxia in the premature-infant—imaging findings. *American Journal of Neuroradiology*, **16**: 1837–1846, 1995.
7. Sawada, H., Udaka, F., Seriu, N. *et al.*: MRI demonstration of cortical laminar necrosis and delayed white matter injury in anoxic encephalopathy. *Neuroradiology*, **32**: 319–321, 1990.
8. Falini, A., Barkovich, A. J., Calabrese, G. *et al.*: Progressive brain failure after diffuse hypoxic ischemic brain injury: a serial MR and proton MR spectroscopic study. *American Journal of Neuroradiology*, **19**: 648–652, 1998.
9. Baenziger, O., Martin, E., Steinlin, M. *et al.*: Early pattern recognition in severe perinatal asphyxia: a prospective MRI study. *Neuroradiology*, **35**: 437–442, 1993.
10. Hopkins, R. O., Gale, S. D., Johnson, S. C. *et al.*: Severe anoxia with and without concomitant brain atrophy and neuropsychological impairments. *Journal of the International Neuropsychological Society*, **1**: 501–509, 1995.
11. Gale, S. D., Hopkins, R. O., Weaver, L. K. *et al.*: MRI, quantitative MRI, SPECT, and neuropsychological findings following carbon monoxide poisoning. *Brain Injury*, **13**: 229–243, 1999.
12. Gadian, D. G., Aicardi, J., Watkins, K. E. *et al.*: Developmental amnesia associated with early hypoxic-ischemic injury. *Brain*, **123**: 499–507, 2000.
13. Mañeru, C., Junqué, C., Botet, F. *et al.*: Neuropsychological long-term sequel of perinatal asphyxia. *Brain Injury*, **15**: 1029–1039, 2001.

14. Adams, J. H., Graham, D., Scott, G. *et al.*: Brain damage in fatal non-missile head injury. *Journal of Clinical Pathology*, **33**: 1132–1145, 1980.
15. Verger, K., Junqué, C., Levin, H. S. *et al.*: Correlation of atrophy measures on MRI with neuropsychological sequel in children and adolescents with traumatic brain injury. *Brain Injury*, **15**: 211–221, 2001.
16. Iai, M., Tanabe, Y., Goto, M. *et al.*: A comparative MRI study of the corpus callosum in neurologically normal children and children with spastic diplegia. *Acta Paediatrica*, **83**: 1086–1090, 1994.
17. Njiokiktjien, C., Sonneville, L. D. and Vaal, J.: Callosal size in children with learning disabilities. *Behavioral Brain Research*, **64**: 213–218, 1994.
18. Hiroshi, Y., Hidenao, F., Yasuhiro, N. *et al.*: Atrophy of the corpus callosum, cortical hypometabolism, and cognitive impairment in corticobasal degeneration. *Archives of Neurology*, **55**: 609–614, 1998.
19. Edwards, S. G., Liu, C. and Blumhardt, L. D.: Cognitive correlates of supratentorial atrophy on MRI in multiple sclerosis. *Acta Neurologica Scandinavica*, **104**: 214–223, 2001.
20. Laissy, J. P., Patrux, B., Duchateau, C. *et al.*: Midsagittal MR measurements of the corpus callosum in healthy subjects and diseased patients: a prospective survey. *American Journal of Neuroradiology*, **14**: 145–154, 1993.
21. Witelson, S. F.: Hand and sex differences in the isthmus and genu of the human corpus callosum. *Brain*, **112**: 799–835, 1989.
22. Yamauchi, H., Fukuyama, H., Nagahama, Y. *et al.*: Atrophy of the corpus callosum, cortical hypometabolism, and cognitive impairment in corticobasal degeneration. *Archives of Neurology*, **55**: 609–614, 1998.
23. Giedd, J. N., Rumsey, J. M., Castellanos, F. X. *et al.*: A quantitative MRI study of the corpus callosum in children and adolescents. *Developmental Brain Research*, **91**: 274–280, 1996.
24. Hynd, G. W., Hall, J., Novey, E. S. *et al.*: Dyslexia and corpus callosum morphology. *Archives of Neurology*, **52**: 32–38, 1995.
25. Njiokiktjien, C. and Sonneville, L. D.: Abnormal morphogenesis of the corpus callosum, II: morphometry. In: G. Ramaekers and C. Njiokiktjien (editors) *The child's corpus callosum* (Amsterdam: Suyi Publications), pp. 310–318, 1991.
26. Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R. *et al.*: Corpus callosum morphology in attention-deficit-hyperactivity disorder: morphometric analysis of MRI. *Journal of Learning Disabilities*, **24**: 141–146, 1991.
27. Atkinson, D. S., Abou-Khalil, B., Charles, P. D. *et al.*: Midsagittal corpus callosum area, intelligence, and language dominace in epilepsy. *Journal of Neuroimaging*, **6**: 235–239, 1996.
28. Bookstein, F. L., Streissguth, A. P., Sampson, P. D. *et al.*: Corpus callosum shape and neuropsychological deficits in adult males with heavy fetal alcohol exposure. *Neuroimage*, **15**: 233–251, 2002.
29. Pujol, J., Vendrell, P., Junqué, C. *et al.*: When does human brain development end? Evidence of corpus callosum growth up to adulthood. *Annals of Neurology*, **34**: 71–75, 1993.
30. Filskov, S. B. and Boll, T. J.: A standardized version of Luria's neuropsychological tests. In: S. Filskou and T. J. Boller (editors) *Handbook of Clinical Neuropsychology* (New York: Wiley-Interscience), Vol. 1, pp. 608–642, 1981.