ASSOCIATED BRAIN ABNORMALITIES IN PATIENTS WITH CORPUS CALLOSUM ANOMALIES*

*Hasan Tekgül MD**, Gülşen Dizdarer MD**, Osman Yalman MD****
*Nuri Şener MD****, Nilgün Yünten MD****, Sarenur Tütüncüoğlu MD******

SUMMARY: Tekgül H, Dizdarer G, Yalman O, Şener N, Yünten N, Tütüncüoğlu S. (Neurology Unit, Department of Pediatrics, Ege University Faculty of Medicine, İzmir, Turkey). Associated brain abnormalities in patients with corpus callosum anomalies. Turk J Pediatr 1999; 41: 173-180.

Forty-nine patients with corpus callosum (CC) anomalies were evaluated in terms of the clinical features and magnetic resonance imaging (MRI) findings. CC anomalies were classified as CC agenesis: 6 (12%), CC hypogenesis: 5 (10%), and CC hypoplasia: 38 (78%). In the CC hypoplasia group the mean value of the genu thickness of the CC was 0.29 ± 0.1 cm, which was less than the normal value of the age-matched normal children (normal range: 0.6-1.2 cm). The associated brain abnormalities were in five distinct groups: gray matter abnormalities, white matter abnormalities, midline brain structure defects, cortical atrophy, and encephalomalacia. There was no uniformity for the clinical spectrum of CC anomalies. Microcephaly, developmental delay and seizures were the prominent findings in patients. The clinical features were more severe in cases with associated brain anomalies. *Key words: corpus callosum, magnetic resonance imaging, brain abnormalities.*

The corpus callosum (CC), a major associative pathway between the cerebral hemispheres, develops between 10-20 weeks of gestation. At the end of ninth months of infancy it has a similar appearance to that in adults. Any insult to the brain during this period of gestation results in an abnormality of the CC. Infectious agents, radiation, chemical agents, maternal hormones, nutritional deficiencies, hypoxia, and chromosomal and genetic factors have all been considered in the etiology of CC anomalies[1-5].

Cranial computed tomography (CT) and magnetic resonance imaging (MRI) have been used to evaluate the anomalies of the CC[6-15], but MRI provides better contrast resolution and the multiplanar imaging that facilitates the definition of these anomalies. Recently CC anomalies were classified by Jinkins et al.[8] as: 1) CC agenesis (a-initiative agenesis, b-obstructive agenesis), 2) CC hypogenesis-partial agenesis (a-interruptive agenesis, b-obstructive agenesis), and 3) CC hypoplasia.

* From the Neurology Unit, Department of Pediatrics, Ege University Faculty of Medicine, İzmir.

** Pediatrician, Ege University Faculty of Medicine.

*** Radiologist, Ege University Faculty of Medicine.

**** Professor of Radiology, Ege University Faculty of Medicine.

***** Professor of Pediatrics, Ege University Faculty of Medicine.

Although isolated anomalies of the CC may not cause significant functional deficits, severe neurological deficits have been reported in patients also having other cerebral anomalies[1, 8, 13]. In this study we evaluated the clinical features and associated brain abnormalities in patients with corpus callosum anomalies.

Material and Methods

The MRI scans of 328 patients followed up as Pediatric Neurology outpatients between 1991-1996 reevaluated. Each MRI image utilizing T1 and T2-weighted spin-echo technique in sagittal, axial and/or coronal planes was reviewed. Corpus callosum CC anomalies were classified as agenesis, hypogenesis or hypoplasia based on the presence or absence of the corpus callosum portions (genu, body, splenium, and rostrum). The corpus callosum CC was totally absent in patients with agenesis and was partially absent in patients with hypogenesis. In the CC hypoplasia group, the patients had a diminished width of the CC after its complete formation.

Morphometric measurements of the CC were also made on the midsagittal MRI scans of 38 patients with CC hypoplasia. The genu thickness was measured at a point which fits 1/3 of the anterioposterior of the CC (Fig. 1). Other orthogonal images were also evaluated for additional information about the rest of the brain. Magnetic resonance imaging MRI findings and clinical features of the patients were evaluated.

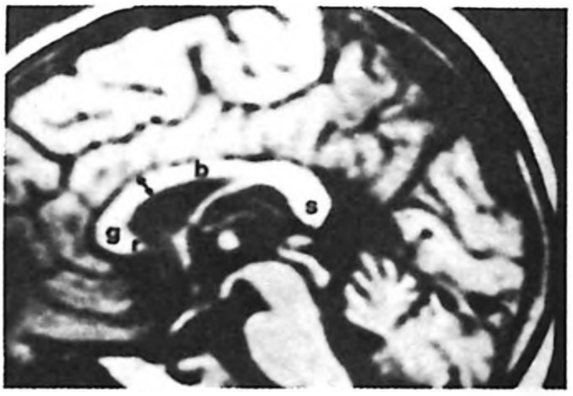

Fig. 1: Measurement of the thickness of genu at the anterioposterior length of the CC. T1-weighted sagittal image shows normal appearance of CC. r: rostrum, g: genu, b: body, s: splenium.

Results

According to MRI scans, CC anomalies were found in 49 of the 328 patients (15%). The corpus callosum was totally absent in six patients (12%) and partial agenesis was evident in five patients (10%) (Figs. 2, 3). Hypoplasia of the CC was found in 38 patients (78%) (Fig. 4) (Table I). Isolated agenesis of the CC was found in only three patients.

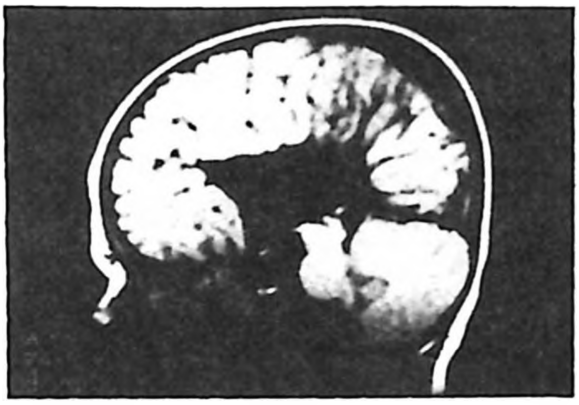

Fig. 2: T1-weighted sagittal image shows absence of the CC.

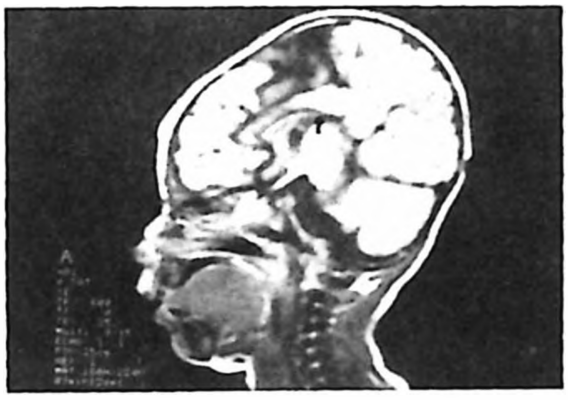

Fig. 3: T1-weighted sagittal image shows severe callosal thinning anteriorly and its absence posteriorly (hypogenesis). Note that the cingulate gyrus overlying the thin callosal structure, falsely appears as a normal corpus callosum.

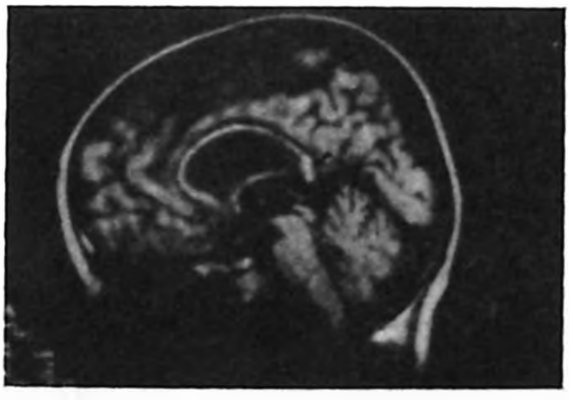

Fig. 4: T1-weighted midsagittal image shows diffusely thinned corpus callosum (hypoplasia). Note the junction of the body and the splenium shows an angle about 90°, creating an hammer appearence indicated by arrow.

In the CC hypoplasia group, genu thickness of the CC was measured at a point which fits 1/3 of the anterioposterior of the CC. The value for each patient was less than the normal range values obtained in the similar age group of Turkish

children, as reported by Oyar et al.[16] (normal range: 0.6-1.2 cm for 1-6 years of age). The mean value of the genu thickness of the CC was 0.29 ± 0.1 cm in patients with CC hypoplasia (Table I).

Table I: Clinical Features of Patients with CC Anomalies

	Agenesis of CC n = 6 (12%)	Hypogenesis of CC n = 5 (10%)	Hypoplasia of CC n = 38 (78%)
Genu thickness of CC (cm)			0.29 ± 0.1
Age (mean: month)	71 ± 29	26 ± 11	50 ± 18
Gender M, F	3, 3	4, 1	24, 14
Parental consanguinity	3 (50%)	4 (80%)	6 (16%)
Asphyxia	1 (17%)	1 (20%)	12 (32%)
Microcephaly	1 (17%)	2 (40%)	17 (45%)
Developmental delay	3 (50%)	4 (80%)	28 (74%)
Seizures	3 (50%)	2 (40%)	23 (61%)
Spasticity	2 (34%)	2 (40%)	11 (35%)
Hypotonia	1 (17%)	1 (20%)	7 (21%)
Optic atrophy	1 (17%)	–	4 (10%)

CC: corpus callosum.

Parental consanguinity was recorded in 80 percent 33 percent and 16 percent of the patients with CC hypogenesis, CC agenesis, and CC hypoplasia, respectively. Perinatal asphyxia, neonatal sepsis and maternal x-ray exposure were found in 43 percent of patients as an insult to the developing brain. Perinatal asphyxia was described in one-third of the patients with CC hypoplasia.

The associated abnormalities in CC anomalies were in five distinct groups: 1) gray matter abnormalities, 2) white matter abnormalities, 3) brain midline structure defects, 4) cortical atrophy and 5) encephalomalacia (Table II). In gray matter abnormalities, neuronal migrational anomalies were found in 10 patients with either CC agenesis or CC hypoplasia pachygyria: 8, schizencephaly: 1, gray matter heterotopia: 1) (Fig. 5). But these associated abnormalities were not found in the group with CC hypogenesis. White matter abnormalities were seen only in patients with CC hypoplasia (periventricular leukomalacia [PVL]: 10, delayed myelination: 6). The defects of the brain midline structures were septo-optic dysplasia (SOD), agenesis of cerebellar vermis, pons hypoplasia, aqueductus stenosis and Arnold-Chiari malformation. Septo-optic dysplasia SOD was found in only CC agenesis and hypogenesis groups. Cortical atrophy and encephalomalacia were frequently observed in patients with CC hypoplasia. Cortical atrophy and encephalomalacia showing diffuse cerebral insult were present in 20/38 (51%) patients with CC hypoplasia.

Microcephaly, developmental delay and seizures were the prominent clinical features in all three groups (Table I). Other clinical findings such as spasticity, hypotonia and optic atrophy were more frequent in patients with CC hypoplasia. Although patients with associated brain abnormalities had severe neurological disabilities, three children with isolated agenesis of the CC had minimal problems in hand skills.

Table II: Associated Brain Abnormalities in CC Anomalies

	Agenesis of CC n=6	Hypogenesis of CC n=5	Hypoplasia of CC n=38
(1) Gray matter abnormalities	pachygyria: 1 schizencephaly: 1 heterotopia: 1		pachygyria: 7
(2) White matter abnormalities			PVL: 10 dm: 6
(3) Midline brain structure defects	SOD: 2 pons hypoplasia: 1 callosal lipoma: 1	SOD: 1 stenosis of aqueductus: 1 agenesis of CV: 1	agenesis of CV: 2 pons hypoplasia: 1 Chiari: 1 malformation
(4) Cortical atrophy	2	1	15
(5) Encephalomalacia		1	5

SOD: septo-optic dysplasia, PVL: periventricular leukomalacia, dm: delayed myelinization, CV: cerebellar vermis.

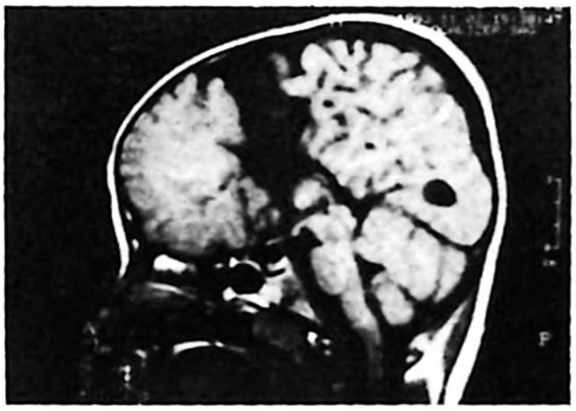

Fig. 5: T1-weighted sagittal image shows agenesis of CC and schizencephalic cleft. The presence of gray matter at the lip of the cleft differenciates the schizencephalic cleft from the interhemispheric cyst.

Discussion

During recent years CC anomalies have been reported as common congenital abnormalities of the central nervous system in childhood[1-15]. In this study we determined the rate of CC anomalies as 15 percent on the basis of MRI evaluation. This rate was higher than the rate detected by CT (2.3%)[1]. Because of the excellent sensitivity due to its superior contrast resolution and multiplanar scans, MRI is superior to CT in detecting these anomalies.

Agenesis and hypogenesis of the CC result from any insult to the developing brain between 10-20 weeks of gestation. Infectious agents, radiation, chemical agents, maternal hormones, and genetic factors have all been considered in the etiology of both primary initiative agenesis and interruptive hypogenesis[6, 8, 13]. The nature of the insult is far less important than the timing of the insult and the genetic susceptibility. In our study, parental consanguinity was more frequent in cases of patients with agenesis (50%) and hypogenesis (80%) of the CC than is present in the average Turkish population (20%). This finding indicates that genetic factors have an important role in agenesis and hypogenesis of the CC. On the other hand, perinatal asphyxia was determined as the most frequent etiologic factor in patients with CC hypoplasia (32%).

Morphometric analysis of the CC has been looked at in different studies[2, 15-19]. Hayakawa et al.[19] reported the mean thickness value (at a point which fits 1/3 of the anterior portion of the CC) as 0.62 ± 0.1 cm in the healthy population. In normal Turkish children the genu thickness was found between 0.6-1.2 cm for children one to six years of age[16]. In our study, we found that the thickness of the CC for each patient was less than the normal range.

Magnetic resonance imaging is preferred for detection of MRI CC anomalies and associated brain lesions. Barkovich and Norman[13] reported associated brain anomalies in half of the patients with CC anomalies. They also reported isolated agenesis of the corpus callosum in only one patient. In our series, isolated CC agenesis was found in three patients, with only minimal problems in hand skills. The remaining three patients in the CC agenesis group had associated brain anomalies with psychomotor retardation, seizures and tonus abnormality.

Neuronal migration anomalies are the most frequent associated gray matter abnormalities in patients with CC anomalies. Neuronal migration is a developmental period of the central nervous system that occurs between eight to 25 weeks of gestation, similar to development of the CC. A severe insult to the brain during this developmental period would explain the association of CC anomalies and neuronal migration anomalies[8, 13].

Septo-optic dysplasia (SOD) is a frequently encountered associated brain abnormality in patients with CC anomalies. Septo-optic dysplasia was SOD originally described as a pathologically distinct entity characterized by an absent or hypoplastic septum pellucidum and dysplasia of the optic chiasma and optic tracts[21]. Septo-optic dysplasia SOD can be associated with hypopituitary dwarfism. We found SOD in three patients with agenesis or hypogenesis of the CC. They had no finding suggesting pituitary insufficiency that would become overt in time.

There has been no general agreement on the clinical significance of hypoplastic CC[17, 20]. Schaefer et al.[20] reported that hypoplastic CC was not a normal variant and was usually associated with subnormal intellectual function in variable

degrees. In our study we found severe neurological findings such as microcephaly (45%), developmental delay (74%) and seizures (61%) in patients with hypoplastic CC. Spasticity, hypotonia and optic atrophy were also seen in those patients. These severe neurological disabilities may be due to the presence of associated brain abnormalities such as white matter abnormalities (PVL, delayed myelinization), cortical atrophy and encephalomalacia.

In conclusion, no characteristic clinical findings are seen in patients with CC anomalies, and the clinical features are closely related to the associated brain anomalies. The presence of a callosal anomaly strongly suggests an additional brain abnormality.

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