

Outcome in Prenatally Diagnosed Fetal Agenesis of the Corpus callosum

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Key Words

Agenesis of the corpus callosum · Prenatal diagnosis · Prenatal counselling · Associated anomalies · Chromosomal abnormalities

Abstract

This study of the outcome and prognostic factors in prenatally diagnosed agenesis of the corpus callosum (ACC) was undertaken to see if there are any differences between subgroups, what relationship they have to neurodevelopmental outcome and whether this information aids the counselling of parents of fetuses with the condition. The outcome of 14 prenatally diagnosed fetuses with ACC and 61 postnatally diagnosed patients was assessed in terms of clinical problems, developmental milestones and neurological signs; each patient was then given a score out of 10, 0 being a normal outcome and 10 being the worst outcome, i.e. death or termination of pregnancy. Comparing patients diagnosed pre- and postnatally, several similarities were found indicating that the postnatal group can provide useful information about the prenatal group. There was a higher incidence of ACC in males than females. In the prenatally diagnosed patients complete ACC was more common than partial ACC, although this might be because partial ACC was easily missed. Complete ACC has a worse prognosis than partial ACC ($p = 0.001$), and when associated with other anomalies, especially of the central nervous system, the outcome is very bad ($p < 0.01$). The only

neurodevelopmentally normal patients were in the isolated partial ACC group. This study highlights the need to perform a detailed review of fetal anatomy and the desirability of determining the karyotype of the fetus in all newly diagnosed cases of ACC so that as much information as possible is available before parents are counselled about the likely outcome.

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Introduction

The corpus callosum accounts for 11% of the weight of the supratentorial brain. It is the largest and most important of the five midline forebrain commissures, consisting of 180 million decussating axons which connect and facilitate communication between the left and right hemispheres [1]. Fully mature, the corpus callosum is crescent shaped and approximately 10 cm long. It develops in an anteroposterior direction, forming in the midline from the lamina terminalis. The corpus callosum is divided into four parts, beginning anteriorly with the rostrum, then the genu followed by the body curving posteriorly and ending in the splenium, its widest and thickest part. Its axons disperse into the white matter of each hemisphere connecting matching areas of the cortex. All four parts of the corpus callosum are present by the 17th week of gestation [2, 3], but as the fetal brain continues to grow the corpus callosum thickens and this process is only completed posteriorly after birth [2].

Agenesis of the corpus callosum (ACC) was first described by Reil in 1812 [4]. It may be either complete or partial. Many theories have been postulated to explain ACC [5]. Failure of the anterior neuropore to close may lead to absence of the lamina terminalis and the commissural plate, and later the development of ACC. Migrational arrest of callosal neurones is associated with failure of axons to cross the midline. It has been suggested that ACC is due to the diencephalic roof plate expanding in the presence of hydrocephalus, leading to cystic dilatation of the roof of the third ventricle and interfering with callosal growth [6].

ACC has been diagnosed postnatally in children from the 1970s by computerised tomography (CT). Since 1982 it has been increasingly frequently diagnosed in utero by ultrasound [2, 7–10]. Features which are common to both are [10]: (1) dilatation of the third ventricle; (2) upward displacement of the third ventricle, often to the level of the bodies of the lateral ventricles; (3) dilatation of the bodies of the lateral ventricles and occipital horns, leading to 'colpocephaly' or 'teardrop ventricular atria'; (4) separation of the frontal horns and bodies of the lateral ventricles and a wide interhemispheric fissure; (5) a concave medial border of the frontal horns; (6) absence of the septum pellucidum and the corpus callosum.

Radial distribution of the sulci on the medial hemispheric surfaces is commonly seen. The significance of this is not known, but it may be a mechanical consequence of the absence of the corpus callosum [11].

Aetiological factors implicated in the pathogenesis of ACC are toxic and metabolic causes, such as alcohol [2, 12, 13], vascular lesions and infectious agents [6], and chromosomal and genetic factors. ACC is frequently associated with trisomies 8, 11, 13, 14, 15 and 18, as well as some other less common chromosomal abnormalities [2]. Recently [14], a gene involved in the development of the corpus callosum has been located on the short arm of chromosome 8.

Many syndromes are associated sporadically with ACC. It is a characteristic of Aicardi, Andermann, Shapiro and acrocallosal syndromes [15–20]. The clinical presentation of ACC is varied. The reported incidence of asymptomatic cases was as high as 23 out of 170 in one study [6]. Jeret et al. [2] believed that the number of asymptomatic cases might be higher since they cannot all be identified clinically. In one prenatal series [21], 7 out of 8 isolated cases were clinically normal.

The clinical presentation is non-specific and has been regarded by many to be related to the associated anomalies rather than ACC itself [2, 6, 16, 18]. Seizures, mental

retardation, developmental delay, microcephaly, macrocephaly and abnormal neurological signs are frequently reported in children with ACC [2, 6, 17, 22].

Incidences of 85% of associated CNS anomalies and 62% of extra-CNS anomalies with ACC have been reported [23], although one study found the incidence to be as low as 36% [15]. The most frequently reported associated abnormalities are hydrocephalus, the Arnold-Chiari malformation and microcephaly [2]. Spinal, craniofacial and limb abnormalities are also common associates with ACC [2, 16, 17], and include spina bifida, scoliosis, talipes equinovarus, polysyndactyly [15], craniosynostosis and cleft lip and palate. Associated congenital cardiovascular, renal and gastro-intestinal abnormalities also occur.

Because ACC is associated with many different abnormalities leading to a varied clinical presentation, the prognosis for fetuses diagnosed prenatally is uncertain, making prenatal counselling difficult. For the parents of an affected fetus to be able to make the decision about whether to continue or terminate the pregnancy, they need information about the likely outcome. Since ACC may also be asymptomatic or cause only subtle neurological abnormalities, this further compounds the difficulty of predicting outcome. This study was designed to see if there are any markers of good and bad outcome that can be identified and associated specifically with complete and partial ACC.

Materials and Methods

Fourteen cases of prenatally diagnosed ACC were compared with 61 postnatally diagnosed cases. The prenatal group was obtained by reviewing the scan reports from the Fetal Management Unit at St. Mary's Hospital, Manchester. Between 1991 and 1998, all cases of complete and partial ACC were identified (table 1). Ultrasound reports and case notes were reviewed for the prenatally diagnosed patients. No information was available for 1 patient, who was excluded from the study. Of the remaining 14, 6 were terminations of pregnancies (TOPs) but were included in the study because valuable information was available about them.

The postnatal group of patients was obtained by reviewing all the CT and MRI scan reports in Booth Hall Children's Hospital of in-patient or out-patient children scanned between 1990 and 1998. Indications for CT or MRI include head injury, epilepsy or neurological abnormalities. CT and MRI scans and the clinical case notes of all the postnatally diagnosed cases were reviewed with a consultant neuroradiologist. Three cases were excluded because the scans were unavailable and a further 36 because the original diagnosis of ACC was incorrect or in doubt. A further 5 cases were excluded because they had shunted hydrocephalus or lobar holoprosencephaly and were judged to have a 'pseudo-agenesis', i.e. secondary loss of the corpus callosum due to the primary condition. In 9 cases, insufficient information was available, so they were excluded (table 1).

Information from ultrasound, CT and MRI scan reports, the clinical case notes, autopsy reports and from a questionnaire completed by the parents or in 26 cases from a formal interview by the author (P.W.A.G.) was documented on a proforma. The information gathered included: (1) time, age and method of diagnosis of ACC; (2) maternal antenatal history; (3) clinical presentation; (4) associated anomalies – including chromosomal and genetic anomalies; (5) family history; (6) developmental milestones for gross motor and fine motor skills, language and hearing, personal and social skills (developmental delay was graded as mild, moderate or severe using the assessment made by either the paediatrician or neurosurgeon in charge when the developmental milestones were not directly available); (7) special educational needs; (8) radiological findings including those of ACC, additional CNS anomalies and abnormalities in other organ systems, and (9) details of a recent neurological examination performed by a paediatrician or neurosurgeon or personally by the author (P.W.A.G.). Dysmorphic features were noted. It must be noted that some information was not available for a small number of cases in the prenatal group.

Each patient was given an outcome score out of 10, 0 for a normal outcome and 10 for the worst possible outcome, death or TOP. TOPs were given a score of 10/10 because the decision to terminate was based on the judgement that the fetus was likely to have a poor outcome. The outcome was scored using clinical presentation, developmental delay and physical signs as follows: (1) the patient was given a score of 1 for each clinical problem, there was a total of 13 possible points; (2) development was graded 1 for mild, 2 for moderate and 3 for severe delay, for each of the developmental categories, gross and fine motor skills, language and hearing and personal and social skills, giving a maximum score of 12; (3) the patients were given a score of 1 if they had hypo-/hypertonia, hyporeflexia, impaired co-ordination, convergent/divergent squint or sensorineural deafness; (4) myopia scored 1 and blindness scored 2; (5) weakness was graded 1 for mild weakness, 2 for moderate weakness and 3 for severe weakness; (6) walking was scored 1 for an abnormal gait and 2 for inability to walk. Out of a final possible total of 41 points, the final outcome score was recalculated as a fraction of 10.

Statistical analysis was performed using the SPSS 6.1.3 program.

Results

Of the 12 prenatal cases where the sex was known there were 7 (58.3%) males and 5 (41.7%) females, the sex of 2 of the TOP cases was not known. The mean age of survival of the liveborn from the group at follow-up was 1.2 years (range 0.25–4.00). In the postnatal group there were 44 (72.1%) males and 17 (27.9%) females, the mean age at follow-up was 5.2 years (range 0.33–18.00). Combining the pre- and postnatal groups there were 51 (69.9%) males and 22 (30.1%) females with a mean age of 4.5 years at follow-up (range 0.25–18.00). The age of TOPs was 0.00 years for the purpose of analysis. In the prenatal group there were 11 (78.6%) cases of complete and 3 (21.4%) of partial ACC. The postnatal group had 34 (55.7%) cases of complete and 27 (44.3%) of partial ACC. Taking both

Table 1. Summary of patients identified and reasons for exclusion

Prenatal group	
15 cases identified initially	
1 case excluded as ultrasound report not available	
6 TOPs remained in the series	
14 patients remained	
Postnatal group	
114 cases identified initially	
3 cases excluded as CT scans were unavailable	
5 cases excluded due to shunted hydrocephalus	
36 cases excluded after incorrect diagnosis of ACC	
9 cases excluded due to lack of information	
61 patients remained	

groups together there were 45 (60%) cases of complete and 30 (40%) of partial ACC. No significant relationship was found between sex and complete or partial ACC. Because there were only 8 prenatal cases, they could only be analysed to a limited extent, but the analysis included outcome and associated anomalies. The cases in both pre- and postnatal groups were divided into six subgroups, complete or partial ACC; these were then further divided into associated CNS anomalies, associated extra-CNS anomalies and isolated ACC (fig. 1, 2).

The Clinical Presentation

The clinical presentation (table 2) of each group recorded from the notes, questionnaire completed by all parents and personal interview were as follows: developmental delay 72.5%, seizures 50.7%, impaired co-ordination 40.6%, mental retardation 39.1%, spasticity 36.2%, visual symptoms 29.0%, macrocephaly 21.7%, microcephaly 17.4%, failure to thrive 15.9%, quadriplegia 14.5%, hemiparesis 11.6%, no symptoms 5.8% and raised intracranial pressure 2.9%. There was no significant difference in presentation between any of the groups.

Associated Anomalies

Fifty-one (68%) out of the 75 patients had associated anomalies; 33 (44%) had CNS anomalies, 22 (29.3%) associated skeletal and craniofacial anomalies, 7 (9.3%) a known syndrome, 6 (8.0%) a chromosomal disorder, 7 (9.3%) a genetic condition, 10 (13.3%) a cardiorespiratory anomaly, 6 (8.0%) a gastro-intestinal anomaly, 3 (4.0%) a metabolic disorder and 2 (2.7%) an associated renal anomaly.

There were no statistically significant differences in the anomalies in the pre- and postnatal groups (fig. 3, 4).

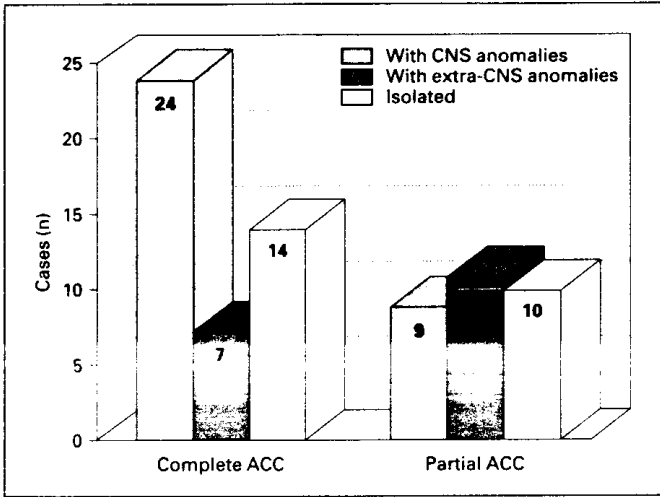


Fig. 1. Number of cases in each subgroup of ACC in the whole series.

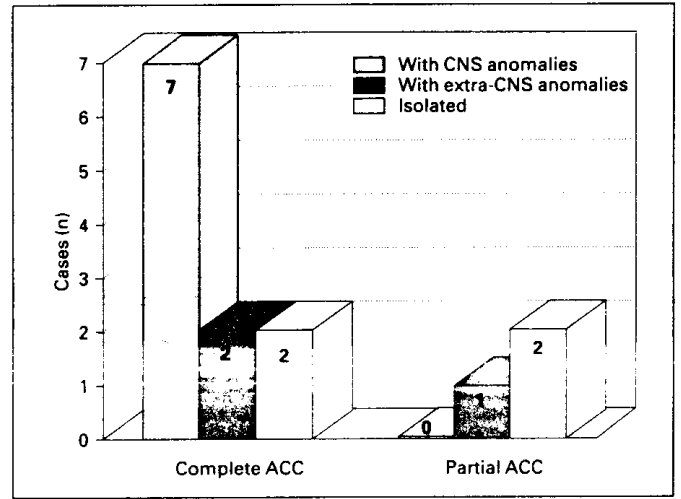


Fig. 2. Number of cases in each subgroup of ACC in the prenatal series.

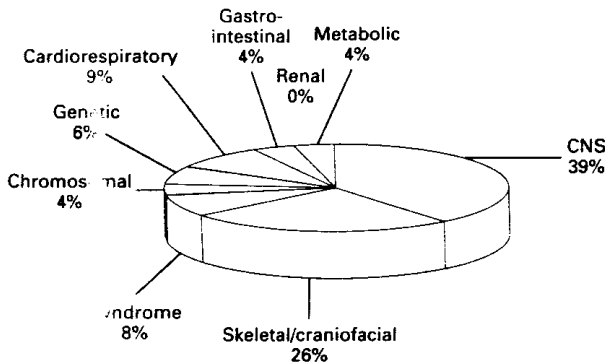


Fig. 3. Frequencies of associated anomalies in the postnatal series.

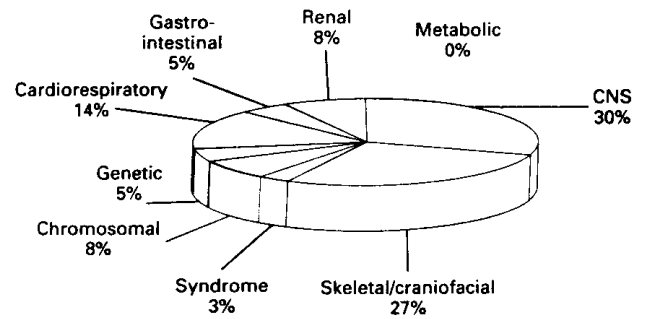


Fig. 4. Frequencies of associated anomalies in the prenatal series.

Outcome

Analysing the pre- and postnatally diagnosed patients together using a one-way ANOVA test, a highly significant relationship was found between the outcome score and the subgroups of ACC ($p = 0.000$). Further analysis using a Scheffé test with significance levels of 0.05 showed that there was a significant difference in the outcome score between the subgroup of complete ACC with associated CNS anomalies and those with complete and partial isolated ACC. No significant relationship between outcome score and age at diagnosis ($p = 0.06$) was found using a Spearman correlation, and no significant relationship between outcome score and sex was found using an independent samples t test. The outcome score was not normally distributed.

The outcome in the prenatally diagnosed cases alone was analysed using the same tests. No significant difference was found in their outcome compared with the whole series, but the mean outcome score was generally worse with the exception of the subgroup of partial ACC with associated CNS anomalies which had a good mean outcome of 0.24. There were no cases of partial ACC with associated extra-CNS anomalies in the prenatal patients. Outcome scores are shown in figures 5 and 6.

In the series as a whole there was no significant relationship between a positive family history of ACC, developmental delay, learning difficulties, epilepsy, other congenital abnormalities and outcome. In the prenatal cases there was no correlation between pregnancy complications, maternal hypo- or hypertension, maternal infections, mater-

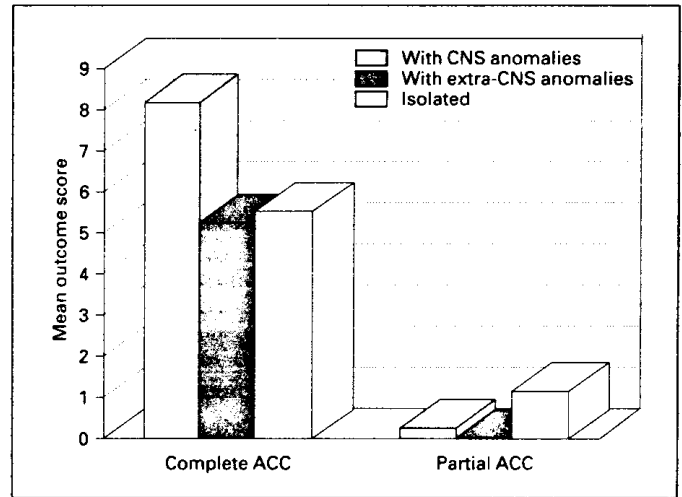
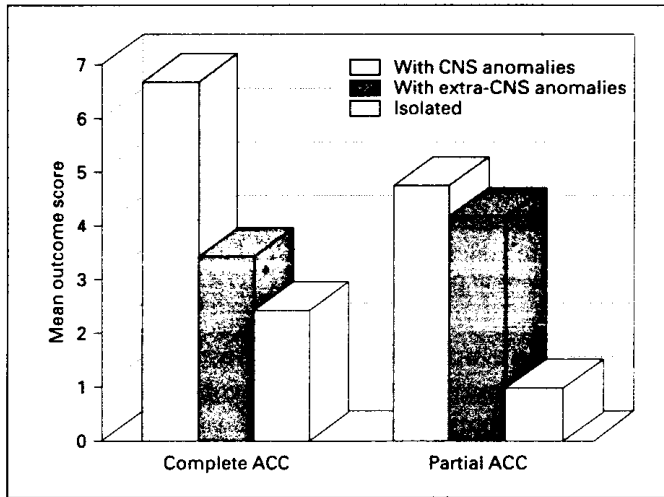


Fig. 5. Mean outcome scores in the subgroups of ACC for the whole series.

Fig. 6. Mean outcome scores in the subgroups of ACC in the prenatal series.

Table 2. Clinical presentations of ACC

ACC group	Presentation												
	no symptoms	seizures	imp. co.	vis. sym.	dev. del.	ment. ret.	macro.	micro.	spast.	hemi.	quad.	↑ ICP	F to T
Com/CNS	0	15 (21.7)	8 (11.6)	7 (10.1)	19 (27.5)	12 (17.4)	3 (4.3)	7 (10.1)	14 (20.3)	2 (2.9)	8 (11.6)	1 (1.4)	3 (4.3)
Com/XCNS	0	3 (4.3)	3 (4.3)	2 (2.9)	4 (5.8)	1 (1.4)	3 (4.3)	0	1 (1.4)	0	0	1 (1.4)	1 (1.4)
Com/Isol	0	5 (7.2)	3 (4.3)	1 (1.4)	7 (10.1)	4 (5.8)	5 (7.2)	1 (1.4)	0	3 (4.3)	0	0	0
Par/CNS	0	5 (7.2)	7 (10.1)	6 (8.7)	8 (11.6)	4 (5.8)	1 (1.4)	1 (1.4)	5 (7.2)	1 (1.4)	2 (2.9)	0	1 (1.4)
Par/XCNS	0	4 (5.8)	4 (5.8)	3 (4.3)	9 (13.0)	6 (5.8)	2 (2.9)	2 (2.9)	5 (7.2)	2 (2.9)	0	0	4 (5.8)
Par/Isol	4 (5.8)	3 (4.3)	3 (4.3)	3 (4.3)	3 (4.3)	0	1 (1.4)	1 (1.4)	0	0	0	0	2 (2.9)
Total	4 (5.8%)	35 (50.7%)	28 (40.6%)	22 (29.0%)	50 (72.5%)	27 (39.1%)	15 (21.7%)	12 (17.4%)	25 (36.2%)	8 (11.6%)	10 (14.5%)	2 (2.9%)	11 (15.9%)

Frequency is indicated in parentheses (%).

Com/CNS = Complete ACC with associated CNS anomalies; Com/XCNS = complete ACC with associated extra-CNS anomalies;

Com/Isol = complete ACC, isolated; Par/CNS = partial ACC with associated CNS anomalies; Par/XCNS = partial ACC

with associated extra-CNS anomalies; Par/Isol = partial ACC, isolated; imp. co. = impaired co-ordination; vis. sym. = visual symptoms;

dev. del. = developmental delay; ment. ret. = mental retardation; macro. = macrocephaly; micro. = microcephaly; spast. = spasticity;

emi. = hemiparesis; quad. = quadriplegia; ↑ ICP = raised intracranial pressure; F to T = failure to thrive.

nal diabetes and epilepsy and outcome; neither was there a significant relationship between outcome and history of miscarriage, stillbirth and sudden infant death.

Scan Findings

Ultrasound, CT and/or MRI scan findings were available for all 75 patients in the series. Sixty (85.3%) had widely separated anterior horns, 55 (73.3%) a 'teardrop' ventricular atrium, 50 (66.7%) a raised third ventricle, 30 (40%) an absent septum pellucidum and 20 (26.7%) a wide interhemispheric fissure. Using the χ^2 and t tests for

independent samples, no significant relationship was found between any of the scan findings and the various subgroups of ACC.

Intellectual Performance

Twenty-seven (57.4%) of 47 school age children in the series were at special schools, and 10 (50%) out of the 20 children at a mainstream school were receiving additional help. Thirty-five (74.4%) out of 47 school age children had been seen by an educational psychologist, and a statement of special needs had been made.

Discussion

The reported prevalence of ACC depends on the population studied and the method of diagnosis. Jeret et al. [24] reported an incidence of 2.3% diagnosed by CT scanning in a developmentally disabled population, and a similar figure of 2.9% was found in a group of children suspected of having cerebral abnormalities [24]. The prevalence in an unselected normal population appears to be much lower, ranging from 0.0005 to 0.7% [24]. The actual frequency in the general population is unknown since asymptomatic cases cannot be identified.

In this series the male-to-female ratio of the 14 prenatally diagnosed patients with ACC was 7:5. The larger number of postnatally diagnosed patients also had a higher male-to-female ratio of 3:1. This finding is consistent with the findings of a large review by Jeret et al. [2], who found a male-to-female ratio of 3:2. Complete ACC was four times more common than partial ACC in the prenatally diagnosed patients. The significance of this figure could be questioned because of the small sample size, but in the series as a whole 60% had complete ACC and 40% partial ACC.

Gupta and Lilford [16] reported that the diagnosis of ACC, in the absence of other sonographically detectable abnormalities, carried an excellent prognosis, with an 85% chance of a normal developmental outcome, and a 15% risk of handicap, although another study [15] showed that only 35% of cases with apparently isolated ACC had a normal outcome. In this study the only statistically significant difference ($p < 0.01$) in outcome was between complete ACC with associated CNS anomalies and the groups complete/partial isolated ACC. Interestingly, complete isolated ACC shows a worse outcome than partial ACC ($p = 0.03$), possibly reflecting the greater disruption of neuronal function in complete ACC.

This study was designed to look for useful predictors of outcome when ACC is diagnosed. Broadly speaking, sex, scan features and associated anomalies can be considered as such.

Vergami et al. [15] reported a better outcome in males than females with isolated ACC; this was thought to be due to the known association between ACC and Aicardi syndrome. No significant relationship between sex and outcome was found in the whole or the prenatal series in this study.

A number of prognostic indicators of outcome in ACC from scan features were identified by Gupta and Lilford [16]. They showed that upward displacement of the third ventricle and a widened interhemispheric fissure fre-

quently accompanied neurological impairment, associated anomalies and poor outcome. There was no correlation between scan findings and outcome in the present series; however, there was a higher incidence of raised third ventricle in the subgroup of complete ACC with associated CNS anomalies, suggesting indirectly that having a raised third ventricle may indicate a poor outcome.

It is widely accepted that ACC is associated with a number of CNS abnormalities [25] as well as syndromes and chromosomal anomalies. Looking at the associated anomalies as a predictor of outcome with ACC offers no real value. However, some useful conclusions can be drawn by comparing the pre- and postnatal groups. The frequencies of associated anomalies in both groups are similar, but there are more CNS anomalies in the postnatal group (39%) than in the prenatal one (30%); more syndromes were also diagnosed postnatally (8%) than prenatally (4%). Both these types of problems are generally associated with a poor outcome. This may indicate that CNS anomalies and syndromes are more frequently missed or that it is not possible to diagnose them prenatally. The high incidence of CNS anomalies, syndromes and many other anomalies associated with ACC emphasises the importance of a detailed review of fetal anatomy and mandatory fetal karyotyping in all prenatally diagnosed cases of ACC. Routine postnatal follow-up is required to detect abnormalities missed or undetectable by fetal ultrasonography.

While this study offers some useful information, there are several limitations which must be highlighted.

Selecting the postnatal group from patients who had a CT brain scan whilst admitted to hospital may have introduced a selection bias as these patients may have had pre-existing neurological problems, hence the reason for the scan in the first place. Secondly the value of the information offered from the prenatal group must be questioned due to its small size. There were incomplete databases on many of the patients, so there was not a uniform evaluation of all patients in the series and finally scoring the TOPs with a mean outcome score of 10 may have been a mistake, as the outcome is not known, had the pregnancy continued. While the study offers some useful information, there are still no useful predictors of outcome, due to the large numbers of variables associated with ACC.

Predicting the outcome for a fetus diagnosed as having ACC remains a problem. This series has compared prenatally diagnosed ACC patients with those diagnosed postnatally and has shown that there are similarities between the two. This has allowed the identification of some prognostic indicators of outcome, which should be useful for the

counselling of parents of affected fetuses. There is little doubt that complete ACC has a worse prognosis than partial ACC. The presence of anomalies with both complete and partial ACC worsens the prognosis, particularly if they are in the CNS. Complete ACC with associated anomalies has the worst outcome closely followed by partial ACC with associated CNS anomalies. Isolated partial ACC has the best prognosis. A poor outcome is associated with a high incidence of seizures, developmental delay, mental retardation and severe abnormal neurological signs. In this series only 4 patients diagnosed either pre- or postnatally had an apparently normal outcome. It has been suggested that there is no such thing as an asymptomatic callosal patient [26]. Even in the absence of serious neurodevelopmental problems, psychological ones may be present.

Further research is needed before any useful predictors of outcome are known, perhaps looking at the quantitative

measurement of the ventricles and corpus callosum and outcome. When the genetic locus for the corpus callosum is found [14], it should improve our understanding of ACC and increase our awareness of the problems these patients are likely to encounter. With greater knowledge of the condition and its consequences, it will be possible to give parents of an affected fetus much needed information to allow them to choose how to manage the pregnancy.

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