Outcomes Associated With Isolated Agenesis of the Corpus Callosum: A Meta-analysis

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abstract

CONTEXT: Antenatal counseling in cases of agenesis of the corpus callosum (ACC) is challenging.

OBJECTIVES: To ascertain the outcome in fetuses with isolated complete ACC and partial ACC.

DATA SOURCES: Medline, Embase, CINAHL, and Cochrane databases.

STUDY SELECTION: Studies reporting a prenatal diagnosis of ACC. The outcomes observed were: chromosomal abnormalities at standard karyotype and chromosomal microarray (CMA) analysis, additional anomalies detected only at prenatal MRI and at postnatal imaging or clinical evaluation, concordance between prenatal and postnatal diagnosis and neurodevelopmental outcome.

DATA EXTRACTION: Meta-analyses of proportions were used to combine data.

RESULTS: Twenty-seven studies were included. In cACC, chromosomal anomalies occurred in 4.81% (95% confidence interval [CI], 2.2–8.4) of the cases. Gross and fine motor control were abnormal in 4.40% (95% CI, 0.6–11.3) and 10.98% (95% CI, 4.1–20.6) of the cases, respectively, whereas 6.80% (95% CI, 1.7–14.9) presented with epilepsy. Abnormal cognitive status occurred in 15.16% (95% CI, 6.9–25.9) of cases. In partial ACC, the rate of chromosomal anomalies was 7.45% (95% CI, 2.0–15.9). Fine motor control was affected in 11.74% (95% CI, 0.9–32.1) of the cases, and 16.11% (95% CI, 2.5–38.2) presented with epilepsy. Cognitive status was affected in 17.25% (95% CI, 3.0–39.7) of cases.

LIMITATIONS: Different neurodevelopmental tools and time of follow-up of the included studies.

CONCLUSIONS: Children wih a prenatal diagnosis of isolated ACC show several degrees of impairment in motor control, coordination, language, and cognitive status. However, in view of the large heterogeneity in outcomes measures, time at follow-up, and neurodevelopmental tools used, large prospective studies are needed to ascertain the actual occurrence of neuropsychological morbidity of children with isolated ACC.

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Agenesis of the corpus callosum (ACC) is one of the most common congenital brain anomalies, with an estimated prevalence ranging from 1.8 per 10 000 in the general population to 230–600 per 10 000 in children with neurodevelopmental disabilities.[1–3]

Neurodevelopmental outcome for individuals with callosal abnormalities is extremely variable even between children sharing similar neuroanatomic profiles, and there is often significant overlapping in the neuropsychological performance between patients with complete ACC (cACC) and those with partial ACC (pACC).[4] Delay in motor and cognitive functions, epilepsy, and social and language deficits are the most common symptoms reported in individuals with ACC; furthermore, ACC has been linked with the occurrence of autism, schizophrenia, and attention-deficit disorders.[5–9] However, pediatric series are biased by the fact that only symptomatic cases are reported.

Advances in prenatal imaging techniques have led to an increase the detection rate of ACC; however, antenatal counseling when a fetus is diagnosed with this anomaly is still challenging.[5]

Chromosomal abnormalities are common in ACC, especially when associated anomalies are present, and prenatal invasive tests are usually performed in pregnancy to rule out aneuploidies. Chromosomal microarray (CMA) allows the detection of small genomic deletions and duplications that are not routinely seen on standard cytogenetic analysis (copy number variations [CNVs]). Fetuses with central nervous system (CNS) anomalies and normal karyotype have been shown to have a significantly higher risk of genetic anomalies at CMA analysis; however, the risk of clinically significant CNVs in fetuses with isolated callosal anomalies has not been completely ascertained yet.[10,11]

Antenatal MRI is usually performed to rule out associated anomalies, which are major determinants of outcome in cases of ACC; however, the actual diagnostic accuracy of fetal MRI in isolated ACC is still debated.[12]

Neurodevelopmental outcome in fetuses with isolated ACC has been reported to be normal in a large majority of cases, especially in complete agenesis. However, a precise categorization of the burden of neuropsychological disabilities is required to counsel parents more appropriately.[13]

The first aim of this systematic review was to ascertain the rate of associated genetic or anatomic abnormalities in those patients with an initial ultrasound examination showing isolated ACC; the secondary aim was to explore the neurodevelopmental status of these children.

METHODS

Protocol, Eligibility Criteria, Information Sources, and Search

This review was performed according to an a priori designed protocol and recommended for systematic reviews and meta-analysis.[14,15] Medline, Embase, CINAHL, and Cochrane databases were searched electronically on February 15, 2014 using combinations of the relevant medical subject heading terms, key words, and word variants for "agenesis of the corpus callosum" and "outcome"; the search was then updated on November 26, 2015 (Supplemental Table 5). The search and selection criteria were restricted to English. Reference lists of relevant articles and reviews were hand searched for additional reports. PRISMA guidelines were followed.[16]

Study Selection, Data Collection, and Data Items

Studies were assessed according to the following criteria: population, type of callosal agenesis (cACC and pACC) outcome, type of imaging assessment, and outcome (Table 1).

Two authors (F.D. and G.P.) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full-text copies of those papers were obtained and the same 2 reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached with a third author. If >1 study was published for the same cohort with identical end points, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies (Table 2). According to NOS, each study is judged on 3 broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment outcome of interest.[44] Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and the demonstrating that outcome of interest was not present at the start of the study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts on the basis of the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of assessment of the outcome of interest, length, and adequacy of

TABLE 1 General Characteristics of the Included Studies

Source	Year	Country	Study Design	Type of ACC	Prenatal Imaging	Fetuses (*n*)	Isolated ACC (*n*)	Dedicated Neurodevelopmental Tool	Length of Follow-up
Cesaretti (17)[a]	2015	Italy	Retrospective case series	Complete	US, MRI	62	62	NA	NA
Ruland (18)[a]	2015	Germany	Retrospective case series	Complete, partial	US, MRI	127	39	NA	Not reported
Papoulidis (19)	2015	Greece	Retrospective case series	Complete, partial	US	4	2	NA	NA
Shen (20)[a]	2015	France	Retrospective case series	Partial	US, MRI	77	35	NA	NA
Pashaj (21)	2015	Albania-Germany	Retrospective case series	Complete, partial	US	33	6	NA	3–6 mo
Özyüncü (22)[a]	2014	Turkey	Retrospective case series	Complete, partial	US, MRI	33	16	NA	NA
Lachmann (23)	2013	United Kingdom	Retrospective case series	Complete	US, MRI	15	7	NA	NA
Kasprian (24)[a]	2013	Austria	Prospective case series	Complete, partial	US, MRI	20	12	NA	NA
Yinon (25)[a]	2013	Israel	Retrospective case series	Complete, partial	US, MRI	4	4	NA	NA
Vestergaard (26)[a]	2013		Retrospective case series	Complete, partial	US	4	2	NA	NA
Moutard (27)[a]	2012	France	Prospective case series	Complete, partial	US, MRI	17	17	Wechsler Intelligence Scale for Children (III), Dellatolas Protocol, Pegboard Test, Rey-Osterrieth Complex Figure Test	10 y
Wapner (28)[a]	2012	United States	Prospective case series	Complete, partial	US	15	3	Not performed	NA
Yamasaki (29)[a]	2012	Japan	Retrospective case series	Complete	US	10	8	Standard neurologic examination	Not specified
Shaffer (30)[a]	2012	United States	Retrospective case series	Complete, partial	US	69	45	NA	NA
Mangione (31)	2011	France	Prospective case control study	Complete, partial	US, MRI	112	112	CDI (Ireto's Child Developmental Inventory)	4 y (30–74 mo)
Ghi (32)	2010	Italy	Retrospective case series	Partial	US, MRI	14	10	Standard neurologic examination	2–10 y
Cignini (33)	2010	Italy	Prospective case series	Complete	US	17	15	Binet-Simon Scale revided from Stanford	4 y
Tang (34)[a]	2009	United States	Retrospective case series	Complete	US, MRI	10	4	Not performed	2–23 mo
Goetzinger (35)	2009	United States	Retrospective case series	Complete	US	9	3	NA	NA

TABLE 1 Continued

Source	Year	Country	Study Design	Type of ACC	Prenatal Imaging	Fetuses (*n*)	Isolated ACC (*n*)	Dedicated Neurodevelopmental Tool	Length of Follow-up
Chadie (36)	2008	France	Retrospective case series	Complete, partial	US, MRI	13	13	Brunet-Lenzine test revised for children, Wechsler Preschooland Primary Scale of Intelligence, Wechsler Intelligence Scale for Children-III, Terman-Merril Scale	3–16 y
Fratelli (37)[a]	2007	United Kingdom	Retrospective case series	Complete, partial	US, MRI	117	37	Standard neurologic examination	3 y (1–5 y)
Pisani (38)	2006	Italy	Prospective case series	Complete, partial	US, MRI	9	7	Griffiths Scales of Mental Development , Welchler primary, preschool and children scales	2–16 y
Ramelli (39)	2006	Switzerland	Retrospective case series	Complete	US	3	3	Wechsler intelligence Scale for Children-revised, Griffiths Scales of Mental Development	2–10 y
Volpe (40)	2006	Italy	Retrospective case series	Partial	US, MRI	19	9	Standard neurologic examination	1–6 y
Blaicher (41)	2003	Austria	Retrospective case series	Complete, partial	US, MRI	4	4	Standard neurologic examination	Not specified
Malinger (42)[a]	2002	Israel	Retrospective case series	Complete, partial	US, MRI	8	5	Standard neurologic examination	Not specified
Goodyear (43)	2001	United Kingdom	Retrospective case series	Complete, partial	US, MRI	14	4	Standard neurologic examination	Not specified

NA, not assessed; US, ultrasound.
[a] Additional information provided by the authors.

follow-up. According to NOS, a study can be awarded a maximum of 1 star for each numbered item within the Selection and Outcome categories. A maximum of 2 stars can be given for the Comparability category.[44]

Risk of Bias, Summary Measures, and Synthesis of the Results

The incidence of the following outcomes was analyzed in fetuses with a prenatal diagnosis of cACC and pACC separately:

1. Chromosomal abnormalities detected with standard karyotype analysis.
2. Pathogenic CNVs at CMA.
3. Rate of additional CNS anomalies detected only at prenatal MRI but missed at the initial scan.
4. Additional CNS and extra-CNS anomalies detected only at postnatal imaging or clinical evaluation but missed at prenatal imaging.
5. Concordance between prenatal and postnatal diagnosis.
6. Neurodevelopmental outcome.

Only fetuses with a prenatal diagnosis of ACC either by transabdominal or transvaginal ultrasound were included. cACC was defined as the total absence of all the anatomically defined regions of the corpus callosum, whereas pACC was defined as the presence of at least 1 region of the corpus callosum. For the assessment of the incidence of abnormal karyotype, only cases of isolated ACC defined as having no additional CNS and extra-CNS anomalies detected at the ultrasound scan were included in the analysis. Only cases who had their full karyotype tested either prenatally or postnatally were included. For the occurrence of genetic abnormalities detected only at CMA only fetuses with isolated ACC and normal standard karyotype were considered suitable for the analysis. The presence of additional

anomalies detected only at prenatal and postnatal MRI were assessed only in fetuses with no additional anomalies and normal karyotype. For the purpose of this study, mild to moderate ventriculomegaly (defined as a lateral ventricle width ≤15 mm) was not included as an associated cerebral malformation because its development is related to brain re-organization due to callosal agenesis.

The neurodevelopmental outcome of infants with ACC was ascertained exclusively in cases of isolated ACC with normal full standard karyotype and no other SNC and extra-CNS anomalies confirmed postnatally. Cases with isolated ACC confirmed at postnatal imaging but showing extracerebral anomalies at clinical examination were not included in the analysis. Furthermore, because the large majority of the studies showing the contribution of CMA in fetuses with isolated ACC did not report the neurodevelopmental outcome, it was not possible to perform a subanalysis to ascertain the neurologic profile of those cases with normal standard karyotype and no clinically significant CNVs found at CMA.

Neurodevelopmental outcome was divided into 3 different categories (normal, borderline/moderate, and severe) as defined by the original study. Furthermore, to provide a more objective estimation of the neurologic performance of these children, we also assessed the neurodevelopmental outcome in terms of: (1) gross motor control, (2) fine motor control, (3) cognitive status, (4) epilepsy, (5) visual control, (6) sensory status, (7) language, and (8) coordination. All of these figures were ascertained for fetuses with cACC and pACC separately.

Only studies reporting a prenatal diagnosis of ACC were considered suitable for inclusion in the current systematic review; postnatal studies or studies from which cases diagnosed prenatally could not be extracted were excluded. Cases with dysgenesis and/or hypoplasia of the corpus callosum and those with lack of a clear definition of the anomaly were not considered suitable for inclusion. Autopsy-based studies were excluded on the basis that fetuses undergoing termination of pregnancy are more likely to show associated major structural and chromosomal anomalies. Studies reporting the concordance between prenatal and postnatal diagnosis of ACC were excluded unless they provided information about whether the anomaly was isolated or not. Studies of nonisolated cases of ACC were excluded as were studies published before 2000, because we felt that advances in prenatal imaging techniques and improvements in the diagnosis and definition of CNS anomalies make these studies less relevant. Finally, studies that did not provide a clear classification of the anomaly and those that did not differentiate between cACC and pACC were not considered suitable for inclusion in the current review. However, because it was not possible to extrapolate the figures for the occurrence of pathogenic CNVs in fetuses with cACC and pACC separately, this outcome was ascertained in the overall population of fetuses with callosal agenesis.

Only full-text articles were considered eligible for inclusion; case reports, conference abstracts, and case series with <3 cases of ACC, irrespective of whether the anomalies were isolated or not, were also excluded to avoid publication bias.

We used meta-analyses of proportions to combine data.[45] Funnel plots (Supplemental Figs 10, 11, 12, 13, and 14) displaying the outcome rate from individual studies versus their precision (1 per SE) were carried out with an exploratory aim. Tests for funnel plot asymmetry were not used when the

TABLE 2 Quality Assessment of the Included Studies

Author	Year	Selection	Comparability	Outcome
Cesaretti (17)	2015	★★★	★★	★★
Ruland (18)	2015	★★	★	★
Papoulidis (19)	2015	★★★	★★	★★★
Shen (20)	2015	★★	★	★
Pashaj (21)	2014	★★	★	★★
Özyüncü (22)	2014	★★	★	★★
Lachmann (23)	2013	★★	★	★★
Kasprian (24)	2013	★★	★	★
Yinon (25)	2013	★★	★	★★
Vestergaard (26)	2012	★★★	★★	★★★
Moutard (27)	2012	★★	★	★
Wapner (28)	2011	★★★	★★	★★★
Yamasaki (29)	2010	★★★	★★	★★★
Shaffer (30)	2010	★★	★	★★
Mangione (31)	2009	★★★	★	★★
Ghi (32)	2009	★★	★	★
Cignini (33)	2008	★★★	★★	★★
Tang (34)	2007	★★	★	★★
Goetzinger (35)	2006	★★★	★	★★
Chadie (36)	2006	★★	★	★★
Fratelli (37)	2006	★★★	★★	★★★
Pisani (38)	2003	★★	★	★
Ramelli (39)	2002	★★★	★★	★★★
Volpe (40)	2001	★	★	★
Blaicher (41)	2003	★★	★	★
Malinger (42)	2002	★★	★	★
Goodyear (43)	2001	★	★	★★

According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.[44]

total number of publications included for each outcome was <10. In this case, the power of the tests is too low to distinguish chance from real asymmetry.[45,46]

Between-study heterogeneity was explored using the I^2 statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values ≥50% indicate a substantial level of heterogeneity. fixed effects model was used if substantial statistical heterogeneity was not present. In contrast, if there was evidence of significant heterogeneity between studies included, a random effect model was used.[47]

All proportion meta-analyses were carried out by using StatsDirect version 2.7.9 (StatsDirect, Ltd, Altrincham, Cheshire, United Kingdom).

RESULTS

Study Selection and Characteristics

A total of 2296 articles were identified, 153 were assessed with respect to their eligibility for inclusion (Supplemental Table 6), and 27 studies were included in the systematic review (Fig 1) (Table 1).[17–43] These 27 studies included 484 fetuses with isolated ACC and no other associated CNS and/or extra-CNS anomalies at first prenatal assessment.

Quality assessment of the included studies was performed by using NOS for cohort studies.[44] Some of the included studies showed an overall good rate as regard for the selection and comparability of the study groups and for the ascertainment of the outcome of interest. The main weaknesses of these studies were represented by their retrospective design, small sample size , and lack of a standardized postnatal confirmation. Furthermore, the relatively short period of follow-up after birth did not allow a precise estimation of the overall rate of additional anomalies detected only after birth and missed prenatally.

Synthesis of the Results

cACC

Twenty studies including 261 fetuses with isolated cACC were included in this systematic review.

The rate of chromosomal anomalies was 4.81% (95% confidence interval [CI], 2.2–8.4) (Fig 2, Table 3). The figures for the different chromosomal anomalies found in fetuses with isolated cACC are shown in Supplemental Table 7.

It was not possible to extrapolate data for the rate of clinically significant CNVs in fetuses with isolated cACC and normal karyotype, thus the occurrence of clinically significant CNVs was assessed in fetuses with either cACC or pACC.

Overall, the rate of significant CNVs in fetuses with isolated ACC (either cACC or pACC) and normal karyotype was 5.74% (95% CI, 1.3–13.1) (Fig 2).

In 2.99% (95% CI, 0.9–6.1) of the cases, prenatal diagnosis failed in correctly identifying cACC, with some of the cases of pACC misdiagnosed as having cACC (Supplemental Fig 5).

Additional anomalies not detected at prenatal ultrasound were diagnosed at fetal MRI in 7.83% (95% CI, 1.2–19.6) of the cases, whereas the rate of additional structural anomalies diagnosed only after birth and missed at prenatal evaluation was 5.49% (95% CI, 2.4–9.7) (Table 3, Supplemental Figs 6 and 7). Individual case descriptions of the anomalies detected only at fetal MRI and postnatal imaging/ clinical investigation are shown in Supplemental Tables 8 and 9.

In view of the high heterogeneity in study design, age at and type of assessment, and time at follow-up, the rates for abnormal neurodevelopmental outcomes might not reflect the actual neuropsychological performance of these children and should be interpreted with caution. Furthermore, it was not possible to ascertain the neurodevelopmental performance of children with either normal standard full karyotype and no CNVs on CMA because only one study reported this outcome. Neurodevelopmental outcome was reported to be normal in 76.04% (95% CI, 64.3–86.1) of children with a prenatal diagnosis of isolated cACC confirmed at birth (Fig 3, Table 4). The rates of borderline/moderate and severe neurodevelopmental outcome in these children was 16.04% (95% CI, 7.6–26.8,) and 8.15% (95% CI, 2.5–16.8) respectively. Table 3 shows the detailed figures for the abnormal neurodevelopmental performance in children with isolated cACC. Gross and fine motor control were affected in 4.40% (95% CI0.6–11.3) and 10.98% (95% CI 4.1–20.6) of the cases, whereas 6.80% (95% CI, 1.7–14.9) of these children presented with epilepsy. Cognitive status was affected in 15.16% (95% CI, 6.9–25.9) of the cases, whereas language impairment was affected in 8.02% (95% CI, 2.1–17.3). Finally, abnormal ocular control and coordination occurred in 15.84% (95% CI, 4.3–32.9) and 9.50% (95% CI, 3.2–18.7) of the cases, respectively (Supplemental Fig 8).

Individual outcome descriptions of children with isolated cACC showing abnormal neurodevelopmental profiles are shown in Supplemental Table 10.

pACC

Fifteen studies including 225 fetuses with pACC were included in this review.

The rate of chromosomal anomalies in fetuses with pACC and no other structural anomalies visible at prenatal imaging was 7.45% (95%

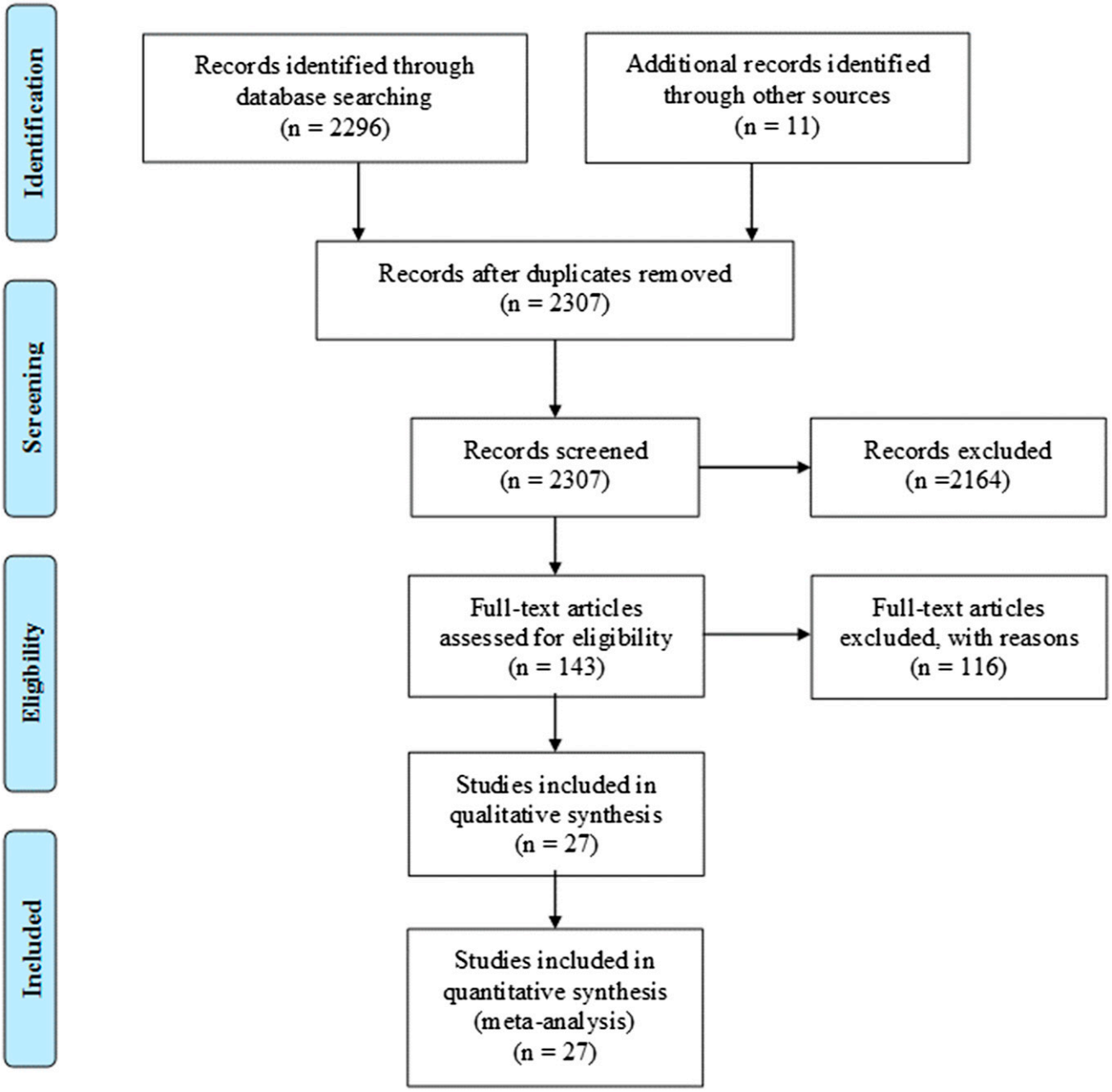

FIGURE 1
Systematic review flowchart.

CI, 2.0–15.9) (Fig 2, Table 4). The figures for the different chromosomal anomalies found in fetuses with isolated pACC are shown in Supplemental Table 11.

Additional anomalies not detected at prenatal ultrasound were diagnosed at fetal MRI in 11.86% (95% CI, 3.2–24.9) of the cases, whereas the rate of additional structural anomalies diagnosed only after birth and missed at prenatal evaluation was 14.46% (95% CI, 6.7–24.6) (Table 4, Supplemental Figs 6 and 7). Individual case descriptions of the anomalies detected only at fetal MRI and postnatal imaging/clinical investigation are shown in Supplemental Tables 12 and 13.

A discrepancy between prenatal and postnatal diagnosis of pACC occurred in 7.99% (95% CI, 2.5–16.3) of the cases, mainly consisting in cases of hypoplastic or dysgenetic corpus callosum misdiagnosed as pACC (Supplemental Fig 5).

Assessment of neurodevelopmental outcome in children with isolated pACC was even more problematic in view of the smaller sample size analyzed compared with cACC.

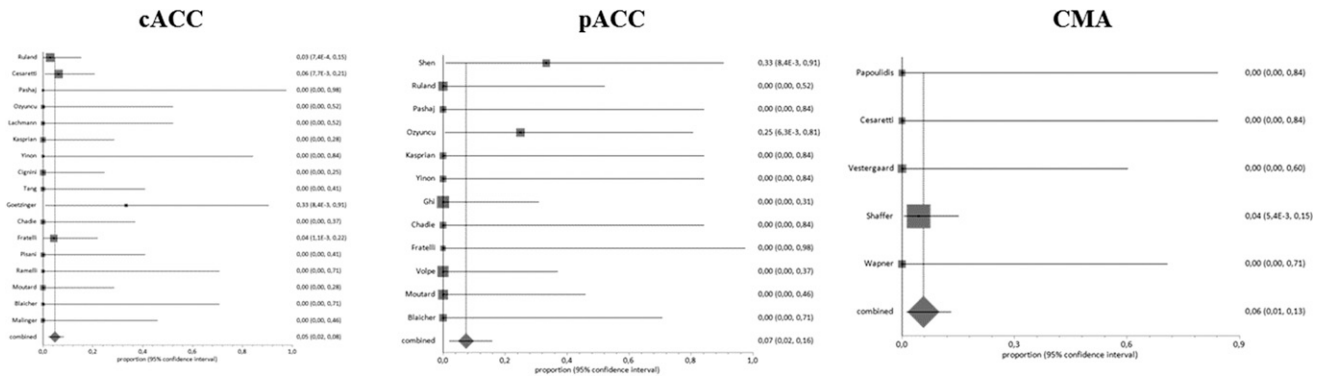

FIGURE 2
Pooled proportions for the occurrence of chromosomal anomalies and pathogenic CNVs in fetuses with cACC and pACC.

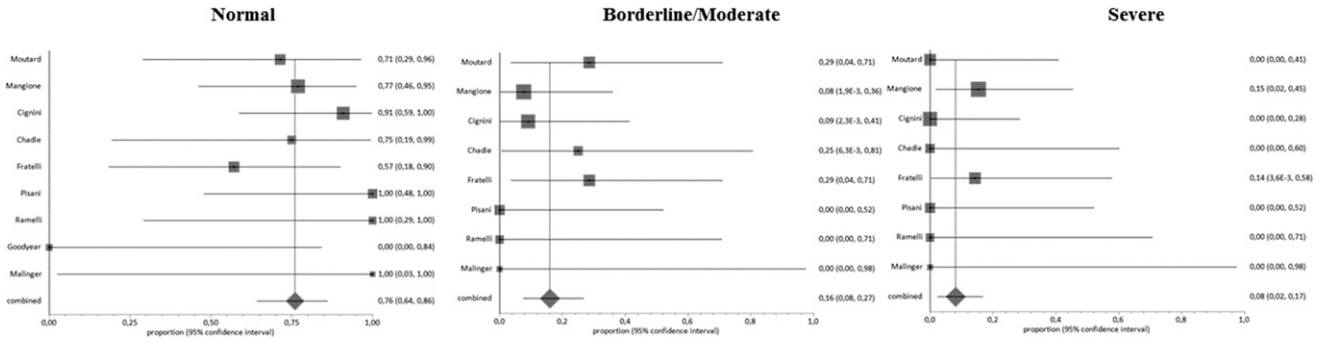

FIGURE 3
Pooled proportions for the occurrence of abnormal neurodevelopmental outcome in fetuses with cACC.

Neurodevelopmental outcome was reported to be normal in 71.42% (95% CI, 53.1–86.7) of children with a prenatal diagnosis of isolated pACC confirmed at birth (Table 4). The rates of borderline/moderate and severe neurodevelopmental outcomes in these children was 14.92% (95% CI, 4.2–30.7) and 12.52% (95% CI, 2.9–27.5), respectively (Fig 4).

Fine motor control was affected in 11.74 (95% CI, 0.9–32.1) of the cases, and 16.11% (95% CI, 2.5–38.2) of these children presented with epilepsy. Cognitive status

TABLE 3 Pooled Proportions for the Outcomes Explored in This Systematic Review in Fetuses With cACC

Outcome	No. of Studies (*n*)	Fetuses (*n*/*N*)	I^2 (%)	Raw % (95% CI)	Pooled Proportion (95% CI)
Pregnancy Outcome					
Chromosomal anomalies (standard karyotype)	17	5/174	0	2.87 (0.9-6.6)	4.81 (2.2–8.4)
Chromosomal microarray (CNVs)[a]	5	2/56	0	3.57 (0.4–12.3)	5.74 (1.3–13.1)
Additional anomalies detected only at prenatal MRI	8	5/99	59.5	5.05 (1.7–11.4)	7.83 (1.2-19.6)
Additional anomalies detected only post-natally	12	9/144	45.9	6.25 (2.9–11.5)	5.49 (2.4–9.7)
Discrepancy between pre and post–natal diagnosis	15	3/156	0	1.92 (0.4–5.5)	2.99 (0.9–6.1)
Neurodevelopmental outcome					
Normal	9	41/53	29.2	77.36 (63.8–87.7)	76.04 (64.3–86.1)
Borderline/Moderate	8	7/51	0	13.73 (5.7–26.3)	16.04 (7.6–26.8)
Severe	8	3/51	0	5.88 (1.2–16.2)	8.15 (2.5–16.8)
Detailed neurodevelopmental outcome					
Gross motor	8	1/51	0	2.0 (0.1–10.6)	4.40 (0.6–11.3)
Fine motor	7	5/50	10.5	10.0 (3.3–21.8)	10.98 (4.1–20.6)
Cognitive	7	7/50	5	14.0 (5.8–26.7)	15.16 (6.9–25.9)
Epilepsy	8	1/51	0	2.0 (0.1–10.6)	6.80 (1.7–14.9)
Sensory	7	0/50	0	0 (0–7.1)	0 (0–9.2)
Visual	7	5/50	52.8	10.0 (3.3–21.8)	15.84 (4.3–32.9)
Coordination	7	5/50	47	10.0 (3.3–21.8)	9.50 (3.2–18.7)
Language	6	4/45	48.3	8.89 (2.5–21.2)	8.02 (2.1–17.3)

[a] The analysis included cases with either isolated cACC and pACC.

TABLE 4 Pooled Proportions for the Outcomes Explored in This Systematic Review in Fetuses With pACC

Outcome	No. of Studies (*n*)	Fetuses (*n*/*M*)	I^2 (%)	Raw % (95% CI)	Pooled Proportion (95% CI)
Pregnancy outcome					
Chromosomal anomalies (standard karyotype)	12	2/48	0	4.17 (0.5–14.3)	7.45 (2.0–15.9)
Chromosomal microarray (CNVs)[a]	5	2/56	0	3.57 (0.4–12.3)	5.74 (1.3–13.1)
Additional anomalies detected only at prenatal MRI	8	3/29	38.7	10.34 (2.2–27.4)	11.86 (3.2–24.9)
Additional anomalies detected only postnatally	10	7/53	1.3	13.21 (5.5–25.3)	14.46 (6.7–24.6)
Discrepancy between prenatal and postnatal diagnosis	9	3/53	0	5.66 (1.2–15.7)	7.99 (2.5–16.3)
Neurodevelopmental outcome					
Normal	7	17/23	0	7.39 (5.2–9.0)	71.42 (53.1–86.7)
Borderline/moderate	7	3/23	0	13.04 (2.8–33.6)	14.92 (4.2–30.7)
Severe	7	2/23	0	8.70 (1.1–28.0)	12.52 (2.9–27.5)
Detailed neurodevelopmental outcome					
Gross motor	4	0/13	0	0 (0–24.7)	0 (0–23.0)
Fine motor	4	1/13	0	7.70 (0.2–3.6)	11.74 (0.9–32.1)
Cognitive	4	2/13	42.2	15.38 (1.9–45.4)	17.25 (3.0–39.7)
Epilepsy	4	2/13	19.4	15.38 (1.9–45.4)	16.11 (2.53.2)
Sensory	4	0/13	0	0 (0–24.7)	0 (0–23.0)
Visual	4	0/13	0	0 (0–24.7)	0 (0–23.0)
Coordination	4	1/13	0	7.70 (0.2–3.6)	11.74 (0.9–32.1)
Language	4	2/13	42.2	15.38 (1.9–45.4)	17.25 (3.0–39.7)

[a] The analysis included cases with either isolated completed and partial ACC.

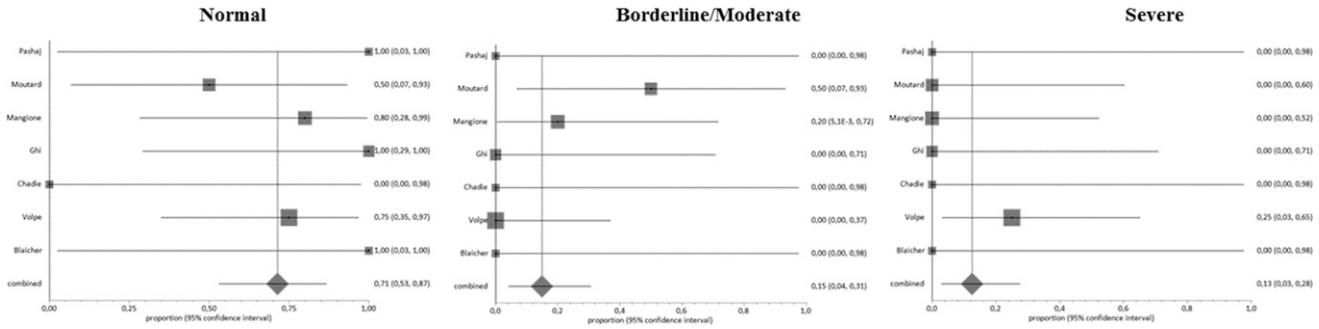

FIGURE 4
Pooled proportions for the occurrence of abnormal neurodevelopmental outcome in fetuses with pACC.

was affected in 17.25% (95% CI, 3.0–39.7) of the cases, whereas language impairment was noticed in 17.25% (95% CI, 3.0–39.7) of the cases. Finally, abnormal coordination occurred in 11.74% (95% CI, 0.9–32.1) of the cases (Supplemental Fig 9).

Individual outcome descriptions of children with isolated pACC showing abnormal neurodevelopmental profile are shown in Supplemental Table 14.

DISCUSSION

Summary of Evidence

The findings from this systematic review showed that fetuses with isolated callosal agenesis (either cACC or pACC) are at high risk of chromosomal anomalies. Even when standard karyotyping is normal, there is still a significant risk of genetic anomalies detected only at CMA analysis. In cases of a prenatal diagnosis of isolated ACC, the risk of associated anomalies detected only at fetal MRI is about 8% and 12% in fetuses with cACC and pACC, respectively, whereas associated anomalies detected only after birth can occur in about 5% of fetuses with cACC and in 14% of those with pACC. Short periods of follow-up, heterogeneity in imaging protocols, neurodevelopmental tools used, discrepancies in the definition of abnormal outcome, and the small number of included cases did not allow us to draw any robust conclusions regarding the occurrence of abnormal neurodevelopmental outcome in children with a prenatal diagnosis of isolated callosal agenesis. The findings from this systematic review suggested that about two-thirds of children showed a normal neurodevelopmental outcome, although fine and gross motor control, coordination, language, and cognitive status can be impaired in a significant proportion of these children. However, these figures might not reflect the actual burden of neuropsychological morbidity in children with isolated ACC; additional large prospective

studies are needed to confirm these findings.

Strengths and Limitations

The strengths of this study are its robust methodology to identify all possible studies, assess data quality, and synthesize all suitable data.

For several meta-analyses, the number of included studies was small and some studies included small numbers. The assessment of the potential publication bias was also problematic, either because of the outcome nature (rates with the left side limited to the value 0), which limits the reliability of funnel plots, or because of the scarce number of individual studies, which strongly limits the reliability of formal tests. Furthermore, all the studies included were retrospective, and thus liable to a considerable risk of selection bias. In addition, several outcomes and associations were not adequately reported in many studies. Finally, because of the relatively short postnatal follow-up period, the overall rate of additional anomalies detected only after birth and missed prenatally may have been underestimated.

The assessment of neurodevelopmental outcome in children with a prenatal diagnosis of isolated ACC was also problematic; differences in age at follow-up and neurodevelopmental tools used did not allow a meaningful stratification of the different outcomes measures; therefore, the figures for the developmental disabilities provided in the current review might not reflect the actual burden of neuropsychological comorbidities associated with isolated ACC and should be interpreted with caution. Furthermore, it was not possible to stratify the analysis including only fetuses with normal standard full karyotype and no pathogenic CNVs detected at CMA in view of the lack of data regarding the neurodevelopmental outcome in these studies. In this scenario, it might be entirely possible that cases with isolated ACC, normal standard karyotype, and pathogenic CNVs were included in the analysis, thus biasing the results. Finally, the majority of the included studies did not report a detailed description of the neurologic performance of fetuses with isolated ACC and merely stratified the analysis in 3 different categories (normal, borderline/moderate, and severe), for which inclusion criteria differed among the studies. In view of all these limitations, the resulting summary measures need to be treated with some caution.

Despite all of these limitations, our review represents the most up-to-date overall assessment of the neurodevelopmental outcome in callosal agenesis diagnosed prenatally; this is important because counseling for parents based on single, small studies that are subject to publication bias may be inadequate.

Implication for Clinical Practice and Future Perspectives

Advances in prenatal imaging techniques have led to an increase in the diagnostic accuracy of ultrasound in detecting callosal anomalies. However, prenatal counseling when a fetus is diagnosed with ACC is challenging.

The findings from this systematic review showed that chromosomal anomalies can occur in a significant proportion of fetuses with isolated ACC; furthermore, the risk of genetic anomalies not detected by conventional karyotyping is also not negligible. CMA has recently been shown to provide useful information in patients with learning disabilities and congenital anomalies for which conventional cytogenetic tests have proven negative. The findings from this review support the use of CMA when ACC is diagnosed prenatally.[48]

Fetal MRI is usually performed in cases of prenatal diagnosis of ACC. In the current review, associated anomalies not detected at ultrasound were diagnosed in 7.83% (95% CI, 1.2–19.6) and in 11.86% (95% CI, 3.2–24.9) in cACC and pACC, respectively. However, even in cases of a prenatal diagnosis of isolated anomaly, the risk of ACC being not truly isolated is relatively high, with additional anomalies detected only at postnatal imaging and/or clinical examination, but missed prenatally, occurring in 5.49% (95% confidence interval [CI], 2.4–9.7) and 14.46% (95% confidence interval [CI], 6.7–24.6) of fetuses with pACC and cACC, respectively.

Quantifying the real contribution of fetal MRI in brain anomalies is challenging. Several factors, such as operator's experience, imaging protocol, time and type of assessment, interval between ultrasound and MRI, and type of anomaly, may play a role in this scenario and explain the wide heterogeneity and the conflicting results reported in previously published studies. Despite all these controversies, MRI is routinely used in clinical practice to confirm diagnosis and to look for associated anomalies. The large majority of additional anomalies detected only at fetal MRI involved neuronal migration disorders (Supplemental Tables 8 and 12), which can be detected preferentially from the third trimester of pregnancy. On this basis, when MRI is performed at the time of the anomaly scan to confirm diagnosis, it might be reasonable to arrange a follow-up scan in the third trimester to ascertain whether ACC is truly isolated. These suggestions are based on the authors' experience and further studies looking at the optimal timing of fetal MRI are needed to confirm these findings.

Furthermore, even when prenatal diagnosis rules out associated anomalies, there is still a significant

risk (5.5% and 14.5% in fetuses with cACC and pACC, respectively) to detect additional anomalies after birth (Supplemental Tables 8 and 12). This should be stressed during antenatal counseling, underlying the fact that prenatal imaging is not always able to differentiate between complex and isolated cases, and that postnatal imaging and a thorough clinical examination are necessary to confirm that ACC is truly isolated.

Assessing the neurodevelopmental profile in children with ACC is challenging. The term neurodevelopmental outcome can be misleading and inappropriate when dealing with brain anomalies because it encompasses a wide spectrum of signs with different underlying disorders and pathologic processes that are not always easily measured and that represent a continuous interaction between pathologic, environmental, and adaptive factors. Intellectual abilities in individuals with ACC have been reported to be in the lower range of normal; furthermore, difficulties in pragmatic language skills and mathematics, expressive and receptive language, visual and spatial reasoning, and attentional skills are impaired or compromised in a significant proportion of children.[5] However, postnatal studies are biased by the fact that only symptomatic patients are included, thus potentially overestimating the burden of disabilities observed in these anomalies.

The findings from this systematic review confirmed these results and showed that children with ACC may present different degrees of impairment in neurologic and neuropsychological domains. Although a direct comparison of the neurodevelopmental and psychological performance of children with cACC compared with those with pACC was not performed in view of the design of most of the included studies, which did not allow such a comparison, the findings of this review do not suggest a huge difference between the 2 different entities of callosal agenesis. The results from this meta-analysis are surprising and disagree with what is observed after birth, where pACC is less likely to be diagnosed as an isolated finding and is usually affected by higher rates of neurodevelopmental disabilities compared with cACC. In the collective authors' opinion, the relatively high rate of favorable outcome observed in pACC might be due to the fact that many of the cases labeled as pACC prenatally are diagnosed after birth as having hypoplasia of the corpus callosum.

CONCLUSIONS

Fetuses with isolated callosal agenesis are at high risk of chromosomal anomalies even when a standard karyotype is negative. Prenatal imaging is not able to completely rule out associated anomalies usually coexisting with this condition, and the risk of ACC of being not truly isolated after birth is significant.

In isolated callosal agenesis, anomalies in fine and gross motor control, coordination, language, cognitive status, and intelligence can occur in a significant proportion of children. However, in view of the small number of included cases, short period of follow-up, and heterogeneity of neurodevelopmental tools adopted, these results should be interpreted with caution, and future large prospective studies aiming at assessing the neurodevelopmental and psychological performance of children with isolated callosal agenesis using standardized tools of neurodevelopmental assessment at appropriate time intervals are needed to ascertain the actual neuropsychological performance and intellectual impairment of children with isolated ACC.

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ABBREVIATIONS

ACC: agenesis of the corpus callosum
cACC: complete agenesis of the corpus callosum
CI: confidence interval
CMA: chromosomal microarray
CNS: central nervous system
CNV: copy number variation
NOS: Newcastle-Ottawa Scale
pACC: partial agenesis of the corpus callosum

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Outcomes Associated With Isolated Agenesis of the Corpus Callosum: A Meta-analysis

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