



## RESEARCH ARTICLE

# Long-term follow-up in a cohort of children with isolated corpus callosum agenesis at fetal MRI

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Received: 30 August 2021; Revised: 11 November 2021; Accepted: 12 November 2021

*Annals of Clinical and Translational Neurology* 2021; 8(12): 2280–2288

doi: 10.1002/acn3.51484

## Abstract

**Objective:** This long-term retrospective follow-up study aimed to address the knowledge gap between prenatal diagnosis of complete isolated Agenesis of Corpus Callosum (cACC) at fetal MRI and postnatal neurodevelopmental outcome to improve prenatal counseling for parents. **Methods:** Data on fetuses with isolated cACC from a single-center MRI database built up in two decades were considered. Detailed postnatal clinical, neuropsychological evaluations were performed and descriptions of available neuroradiological and genetic data were provided. **Results:** Following a detailed neuropsychological evaluation and a long-term follow-up, the subsequent results emerged: 38 school-aged children (older than 6 years) of 50 (aged 2.5–15 years) showed normal intellectual functions (50%), intellectual disability (21%), and borderline intelligence quotient (29%). Deficits in motor functions (58%), executive functions (37%), language (61%), memory abilities (58%), and academic performances (53%) were found. Twenty-one percent of participants showed behavioral difficulties. Almost half of the participants underwent rehabilitation. Additional findings (21%) were detected at postnatal brain MRI, and a significant association between additional findings at postnatal imaging and abnormal neurodevelopmental outcome was observed. **Interpretations:** This study supports the view that children with prenatal diagnosis of isolated cACC may present with several degrees of neurologic and neuropsychological impairment which become more evident only in their second decade of life. Postnatal MRI and detailed genetic analysis may add crucial information to prenatal data and substantially influence final judgment on the outcome and orient clinical management and counseling.

## Introduction

Complete Agenesis of the corpus callosum (cACC) is among the most frequent congenital brain malformations encountered in prenatal diagnosis, either isolated or associated with other intracranial anomalies.<sup>1</sup> The crucial issue of long-term neurological outcomes of isolated ACC at prenatal imaging has been addressed by several studies over the last 2 decades.<sup>2–7</sup> However, an appropriate and satisfactory answer to this has not been provided yet, as

such studies presented with one or more major drawbacks preventing random unbiased recruitment such as, for example, small sample size, limited clinical follow-up, prenatal diagnosis based on ultrasonography (US) only, or case selection based on postnatal imaging.<sup>2,5,6,8–14</sup> Since most skills—that is, language and executive functions—can be fully assessed only during school age, a long-term follow-up with a detailed assessment and appropriate instruments is necessary to properly establish neurodevelopmental outcomes in these patients.<sup>2–7</sup> If suspect findings

are found at US screening, fetal magnetic resonance imaging (MRI) is the gold standard for accurate prenatal neurological diagnosis.<sup>15</sup> It has proven to reliably and consistently detect most cerebral malformations like cortical, commissural, and posterior fossa anomalies, although failing with few conditions such as small nodular periventricular heterotopias.<sup>14–22</sup>

This study considered a large cohort of subjects with isolated cACC as defined by prenatal MRI and carried out a long-term follow-up to address the knowledge gap between prenatal diagnosis of ACC at fetal MRI and postnatal neurodevelopmental outcome, and to improve prenatal counseling for parents.

## Patients and Methods

Fetal MRI has been performed routinely since 2004 at Buzzi Children's Hospital (Milan, Italy) for all suspect cases of cACC after second-level US. In this study, fetal MRIs were performed between 21 and 34 weeks of gestational age, when the basic structure of the corpus callosum is completed. Parents were asked to sign a written consent to be re-contacted after the child's birth in order to collect follow-up information. ACC at prenatal MRI was defined as isolated when there were no other intracranial anomalies except for bilateral mild-moderate ventriculomegaly (10 to 15 mm atrial-width range) which is a common finding present in most ACC cases, especially in the third trimester. Cases of ACC associated with severe ventriculomegaly (>15 mm atrial-width range) or microcephaly were excluded as they were not considered isolated. MRI acquisition and image assessment methods are reported in detail in the Supplemental File.

Briefly, all prenatal 1.5T MRIs included T2-weighted single-shot fast spin-echo (ss-FSE) multiplanar sections while postnatal exams included standard FSE T2-weighted sections, 2D- or 3D T1-weighted and FLAIR sections at 1.5 or 3 T. Of note the prenatal MRI multiplanar image acquisition protocol was not changed since it was first implemented as the same spatial resolution and sequence acquisition parameters were used.

## Clinical assessment

In the time period between January 2015 and January 2019, parents who had agreed to be re-contacted were asked to consent to their children's participation in the study. A clinical questionnaire was administered to 50 responding families by a single certified child psychologist (P.D.S.). Subsequently, children underwent a clinical, neuropsychological evaluation (P.D.S.). Cognitive or developmental levels were assessed by age-appropriate measures: Wechsler Scales (intelligence quotient, IQ) or

Bayley or Griffiths Mental Development Scales (general quotient, GQ). Expressive and receptive language abilities were assessed by age-related specific tests, too. A specific neuropsychological assessment battery evaluating movement, memory, attention, executive functions and behavior was administered (see Supplemental File for the description of assessment tools and related references). All tests were age-appropriate so that results obtained by girls and boys of different ages could still be compared. Fetal MRIs and postnatal brain MRIs were performed by a 1.5 Tesla and 3 Tesla scanner and analyzed by two senior pediatric neuroradiologists (A.R. and C.P. with about 20 years' experience in fetal imaging). A clinical genetic evaluation was performed to identify subjects—among the 50 enrolled participants—with showing a syndromic phenotype so that they could be included in a study with array comparative genomic hybridization (array-CGH) using Agilent Human Genome CGH Microarray Kit 4 × 180 k with an overall median probe space of 13 Kb. Subjects testing negative to array-CGH analysis underwent a next-generation sequencing (NGS) panel of 149 genes known to be more frequently involved in Corpus Callosum Agenesis (see Supplemental File for details).

## Outcome measures

Patients underwent age-appropriate cognitive, motor, and language evaluations. Each cognitive or motor domain was classified as normal, borderline (less than one standard deviation, <1SD), or pathological (less than two standard deviations, <2SD) according to specific test scores or centiles.

## Ethics

The study was approved by the Ethics Committee of E. Medea Scientific Institute. A written informed consent was obtained from all participating families (approval numbers for the study: Study Number 16/19-CE).

## Results

### General results

A cohort of 50 subjects (26 males) ranging in age between 2.5 and 15 years at follow-up (mean age 8.5 years) was enrolled for postnatal evaluation. Pregnancies were normal in 76% of cases, with delivery at term in 82% of cases. The confounding effect of variables (delivery at term / pre-term delivery) was controlled for in the statistical analysis and no significant effect emerged on the outcome. In the four cases (8%) with microcephaly at birth (OFC < 3<sup>rd</sup> centile), at gestational age of MR exam

(21, 21, 29, and 32 weeks, respectively) the cerebral hemisphere biometry was between 10<sup>th</sup> and 50<sup>th</sup> centile. Epilepsy was found in one case. Extra-brain associated findings consisting of minor facial dysmorphisms, nephroptectasis, interventricular septal defect, café-au-lait macules, and profound neurosensory hypoacusis were found in five subjects (10%). The clinical features of the cohort are summarized in Table 1.

## Neuroradiological results

Results of the fetal MRI performed at 21–34 gestational weeks were partially published in a previous study by Cesaratti et al.<sup>23</sup> Commissural malformations were classified into four groups (for details, see the classification in the Supplemental Information): Group 1 (no additional commissure) including 2/50 (4%) patients; Group 2 (anterior commissure (AC) only) including 16/50 (32%) patients; Group 3 (AC and hippocampal commissure (HC)) including 19/50 (38%) patients; Group 4 (AC and residual hybrid structure made up by the fusion of vestigial hippocampal commissure and a very small rudiment of the corpus callosum (HY)) including 13/50 (26%) patients. (Figure 1).

Thirty-three parents (66%) of the initial 50-case cohort undergoing fetal MRI agreed to a postnatal MRI for their children. Participants were distributed in the four categories as follows: Group 1 1/33 (3%); Group 2 14/33 (43%); Group 3 10/33(30%); Group 4 8/33(24%)(Figure S1 in Supplemental File). In 26/33 (79%) participants, the postnatal exam confirmed the same grouping as defined at fetal MRI, with a 100% concordance for Group 4 (Table S1 in Supplemental File). Additional intracranial findings at postnatal MRI were detected in 7/33 (21%) participants: unidentified bright objects (UBOs) in one subject with Neurofibromatosis type I (carrying a *de novo*

del 17q11.2 including *NFI* gene); small periventricular nodular heterotopias in one case; abnormal cerebellar foliation in one case; anterior interhemispheric cyst in two participants; anterior interhemispheric cyst associated with right frontal polymicrogyria in one case; small temporal left arachnoid cyst in one participant (Figure S2 in Supplemental File).

## Genetic results and syndromic features

Of 27 participants with syndromic features tested by array-CGH analysis, 14 subjects (52%) showed normal results while copy number variation (CNV) of unknown significance (VUS) were detected in seven subjects (26%), and *de novo* pathogenic variants were found in the remaining six subjects (22%). These included: three deletions located at 13q32, 17q11.2, and 14q11.2, one duplication at 16p11.2, and two partial trisomy of chromosome 8 in mosaic condition. Next generation sequencing (NGS) gene panel analysis was performed in 21 cases without a pathogenic variant and revealed causative variants in two subjects, consisting of a homozygous variant in *C12orf57* gene in one case and of a *de novo* heterozygous variant in *ZEB2* gene responsible for Mowat–Wilson syndrome in the other. The clinical features of all subjects carrying a pathogenic variant are summarized in the Supplemental File.

## Neuropsychological results

### Development, school performance, and rehabilitation interventions

In the 50-case cohort of enrolled for postnatal evaluation, cognitive and motor developmental outcomes were in the normal range in 62% of subjects, while language development showed the worst functional profile, with only 44% of the subjects in the normal range (borderline development 22% and impaired development 34%). Developmental milestones are summarized in Table 2S (see Supplemental File). School performance was rated as normal in 38 subjects (76%), educational accommodations were provided in seven cases (14%) and individualized curricula were needed in five subjects (10%). Almost half of the patients were attending rehabilitation programs, mainly consisting of speech and motor therapy (45% and 40%, respectively) (Table S3 in Supplemental File).

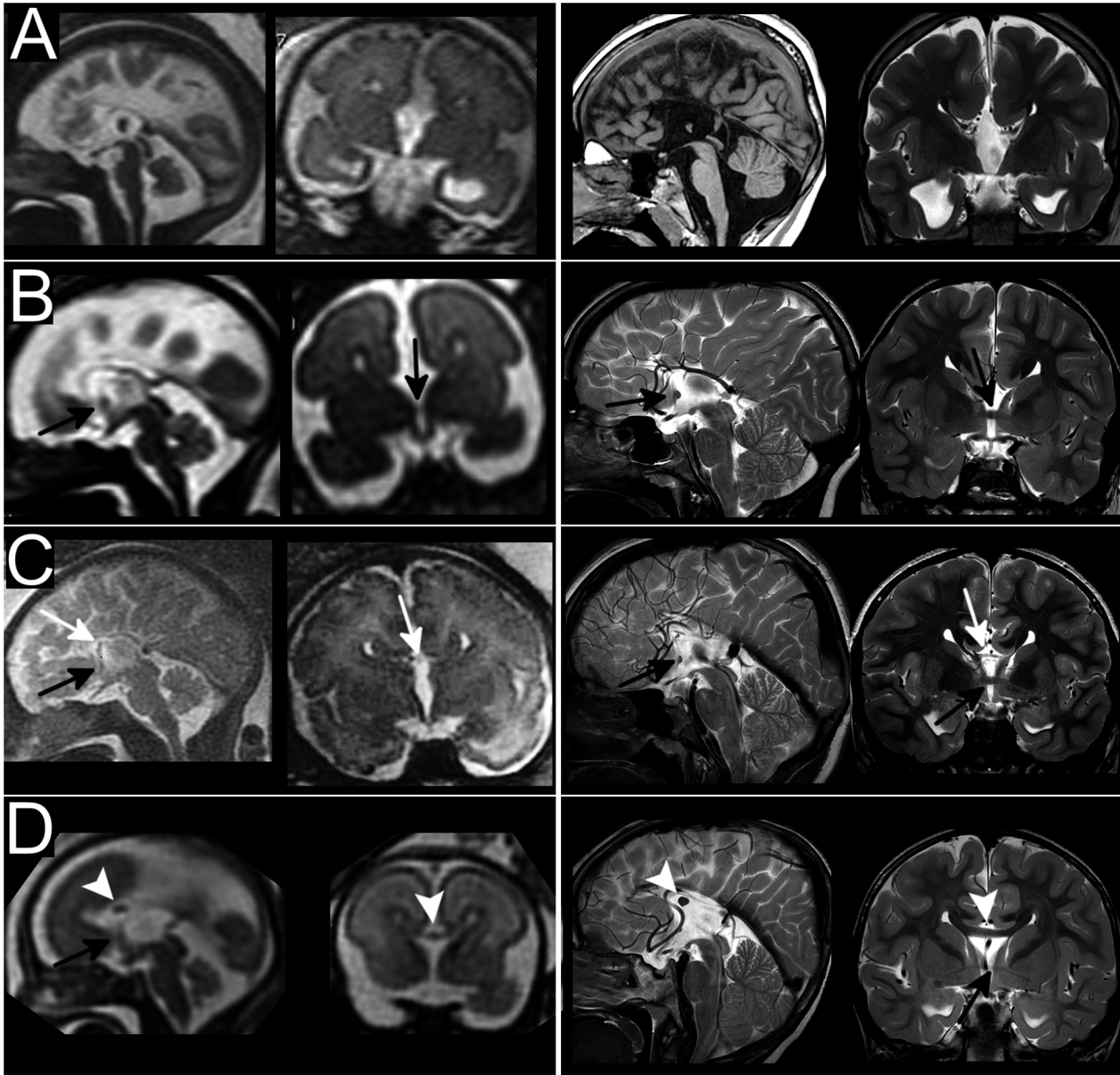
### Neuropsychological and linguistic functions, behavior, academic abilities in school-aged children

A detailed neuropsychological evaluation was performed in the 38 children attending school (older than 6). Overall

**Table 1.** Clinical features of the cohort of the 50 cACC subjects.

Clinical features	N. (total = 50) and percentage
Sex	
Females	26 (52%)
Males	24 (48%)
Normal Pregnancy	38 (76%)
Delivery	
At term	41 (82%)
Preterm	9 (18%)
Eutocic	28 (56%)
Dystocic	5 (10%)
Cesarian Section	17 (34%)
Microcephaly at birth	4 (8%)
Epilepsy during life	1 (2%)
Extra-brain associated findings	5 (10%)
Diagnosis of genetic conditions	8 (16%)

cACC, complete agenesis of corpus callosum; N, number.



**Figure 1.** Examples of MR imaging grouping based on residual interhemispheric commissures. First row (A) shows sagittal and coronal sections (Group 1—patients with no residual commissures), prenatal and postnatal example. Second row (B) example (Group 2—patients with AC), black arrows pointing at AC. Third row (C) example (Group 3—patients with AC), white arrows pointing at HC, besides AC. Fourth row (D) example (Group 4—patients with AC + hybrid residual commissure), arrow head pointing at HY, besides AC.

intellectual functions were in the normal range in half of the participants, while intellectual disability was observed in 21% of them and borderline intelligence quotient in 29%. Fine and gross motor skills were assessed by the Movement Assessment Battery for Children. An impairment in skills was found in 58% of the cases versus 42% in the normal range. Impaired coordination of visual perceptual abilities and fine motor control as assessed by the Developmental test of Visual-Motor Integration was

observed in 42% of the cases, while memory deficits (short- and long-term memory) were found in 58% of the cases. An atypical profile of executive and linguistic functions ranging from borderline to severe impairment was observed in 37% and 61% of the cases, respectively. Behavioral difficulties including deficits in social communication or interaction, deficits in emotional or social control, inhibition, and hyperactivity, were found in 21% of the cases, while academic abilities (reading, writing,

and calculation) were not in the normal range in 53% of the cases. Neuropsychological, linguistic, behavioral, and academic skills are summarized in Table 2. The correlation between fetal MRI and neuropsychological skills is shown in Figure 2. A comparison between fetal and postnatal commissural grouping and neurodevelopmental outcome did not show any significant correlation (see Tables S4A and B in Supplemental File). By contrast, the only significant difference (*p* value <0.05) when comparing MRI findings and neurodevelopmental outcome was the

association between additional intracranial findings at postnatal MRI with an intellectual deficit (Table 3).

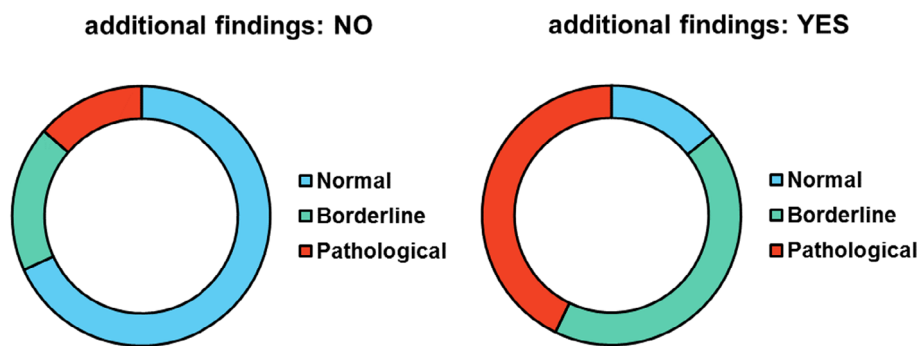
### Discussion

In recent years, advances in prenatal imaging techniques have led to a higher accuracy in the definition of fetal brain malformations, especially midline anomalies including ACC, thereby improving management and counseling.<sup>21,22</sup> Although the detection rate of brain anomalies by fetal US is up to 70–75%, meta-analyses on fetuses with such brain malformations showed that fetal MRI was reliable in 91% of the cases.<sup>12,18–21,24,25</sup> Given that fetal MRI is the most accurate available imaging tool for the assessment of the developing brain and the detection of additional associated cerebral anomalies, minor anomalies can still only be detected at postnatal imaging.<sup>12,16–19,26,27</sup> As the most important factor influencing the prognosis of ACC after an in utero diagnosis is the presence or absence of associated brain (i.e. neuronal migration disorders, interhemispheric cysts, and posterior fossa malformations) and extra-brain anomalies, fetal MRI plays a critical role in predicting neurodevelopmental outcome, with relevant implications for parental counseling and clinical management.<sup>2,8,9,20,22,25,28,29</sup> The present longitudinal retrospective study was designed to

**Table 2.** Neuropsychological, linguistic, behavior, and academic skills in 38/50 subjects over the age of 6 years.

Skills*	Normal	Borderline	Pathological
Intellectual Function	19 (50%)	11 (29%)	8 (21%)
Motor Abilities	16 (42%)	3 (8%)	19 (50%)
Visual-Motor Integration	22 (58%)	0	16 (42%)
Memory	16 (42%)	0	22 (58%)
Executive Functions	24 (63%)	7 (18.5%)	7 (18.5%)
Language	15 (39%)	15 (39%)	8 (22%)
Behavior	30 (79%)	0	8 (21%)
Academic abilities (reading, writing, calculation)	18 (47%)	11 (29%)	9 (24%)

\*For specific and detailed tests see methods section.



**Figure 2.** Correlation between fetal MR imaging and neuropsychological skills.

**Table 3.** Association between additional postnatal MRI findings and neuropsychological skills.

Additional postnatal MRI findings	Neurodevelopmental outcome								
	Motor			Intellectual			Language		
	N	B	P	N	B	P	N	B	P
Yes	50%	21%	29%	68%	18%	14%	28%	28%	44%
No	20%	60%	20%	14%	43%	43%	20%	20%	60%
Chi-square	ns			6.33			ns		
<i>p</i> -value	<0.05								

N = normal; B = borderline; P = pathological; ns = non-significant.

evaluate the prognostic power of fetal MRI in a group of participants recruited in a single center and followed-up for 15 years. Limitations of fetal MRI are known, especially as fetal MRI is performed at a time when brain structures are not fully developed, thus a comparison of fetal and postnatal brain MRI highlights the risk to detect additional anomalies only at postnatal imaging; this risk is reported in about 4–22% of the cases.<sup>2,10,12,30</sup> Even when fetal MRI is performed later during pregnancy—when abnormalities of cortical development may be more accurately detected—many anomalies commonly associated with ACC (reported as a feature in more than 200 different syndromes or metabolic diseases) can be missed. This has important implications for parental counseling, for example, the frequent association between additional anomalies and syndromic conditions has a worse prognosis than isolated cACC.<sup>2,9,28,29</sup>

Our findings are in agreement with all these observations. In our patients undergoing postnatal MRI, additional intracranial findings were detected in 21% of the cases; among these, about one-third of cases showed a syndromic condition. When we compared MRI and neurodevelopmental outcome, a significant difference emerged between additional brain anomalies at postnatal MRI and a cognitive deficit. Indeed, only 14% of the subjects with associated brain anomalies showed normal cognitive functions, while cognitive functions were normal in 68% of cases with isolated ACC. Most of the additional intracranial findings detected postnatally were apparently of minor entity, that is, small interhemispheric and arachnoid cysts, and periventricular nodular heterotopias. It is well-known that these findings are easily missed prenatally. We may only speculate that such minor findings may imply a more generalized brain structural impairment at histological level, a sort of “tip of the iceberg.” Based on our data, the ability of fetal MRI to detect residual interhemispheric commissures was good, since we found a 79% agreement between postnatal MRI characterization of the commissures and prenatal one. However, the presence or absence of commissures, as divided into four groups, did not correlate with the clinical outcome. It cannot be excluded that the sample size was not large enough to establish a possible prognostic value.

Normal results were found in 57% of the subjects undergoing genetic analysis, while variants of unknown significance were detected in 27% of participants. A syndromic condition was diagnosed in 16% of the cases, in line with previous studies reporting an overall rate of chromosomal abnormalities and identifiable syndromes of about 10–19%.<sup>29</sup> All these subjects carrying a syndromic condition displayed an intellectual disability (ranging from mild to severe), suggesting that presence of extra callosal brain anomalies is not the only adverse predictive

factor. Probably, the underlying neurogenetic cause has a stronger effect on clinical phenotype and outcome.<sup>2,8</sup>

The ability to predict long-term neurodevelopmental outcomes in fetuses with evidence of brain malformations is among the main challenges of contemporary medicine. Isolated ACC is a particularly intriguing malformation, given the high heterogeneity of its clinical presentation, the wide variability of clinical manifestation and neuropsychological functioning, and the uncertain prognosis and neuropsychological functioning.<sup>8,11,29</sup> In recent years, several studies attempted to define the long-term neurodevelopmental outcome in subjects with a prenatal diagnosis of isolated ACC.<sup>8–14</sup> Nevertheless, most of them showed several limitations such as lack of fetal MRI (only fetal US was performed), little detailed and standardized cognitive and neuropsychological assessment, and short follow-up (preschool age) or length of follow-up not precisely mentioned.<sup>2,4,5,8–14</sup> Consequently, despite an overall good outcome in over 70% of the cases, children presenting with mild impairment may be missed if not followed up long enough. These children are at risk of mild or late-onset neuropsychological defects as well as learning disabilities or behavioral disorders with school-related difficulties.<sup>3,6,7,13,31,32</sup> Indeed, even if data on early neurodevelopment in our series showed a good outcome (normal range in 62% of subjects) in line with previous evidence,<sup>11</sup> a detailed neuropsychological assessment with specific tests during a standardized long-term follow-up showed that intellectual functions were in normal range only in 50% of participants and less than half had a really normal neuropsychological profile during school-age. Despite the latter, data are only partially consistent with previous reports in our series, deficits became evident over time showing an atypical profile ranging from borderline to severe impairment. In agreement with Siffredi's review,<sup>11</sup> school-related difficulties were found in about one-third of cases which needed individualized curricula and educational or academic accommodation. The behavioral outcome in our population was quite good, in disagreement with previous series, in which a relationship between ACC and behavioral disturbances was documented, especially in older subjects (50–68.2% of the cases).<sup>10,13,31,32</sup> This may be due to the use of an indirect behavioral rating scale administered to parents (Child Behavior Checklist-CBCL).

Almost half of our patients needed a rehabilitation program, lending support to previous findings by Siffredi et al.<sup>13</sup> stressing the importance of a close follow-up and early intervention. Moreover, isolated cACC detected in fetal age is a challenge for rehabilitation, and individually tailored rehabilitation programs are desirable early in life when brain development is characterized by high plasticity.

## Limitations

Despite this being the largest cohort study of subjects with prenatal diagnosis of isolated cACC participating in the longest follow-up to date, some limitations need to be mentioned.

First, 27 parents did not agree to the postnatal MRI study for their children. The lack of these data partially reduced the strength of the study in detecting ethiopathogenesis. Nevertheless, this did not affect the main aim of the study, namely addressing the knowledge gap between prenatal diagnosis of isolated cACC at fetal MRI and postnatal neurodevelopmental outcome. Parental lack of consent was more frequently related to their children's young age and the fact that MRI needed to be performed under general anesthesia.

Second, the gestational age range at MRI was quite wide (21 to 34 weeks) and it might have caused a variability in prenatal diagnostic accuracy, although the seven cases with additional postnatal MRI findings quite an even distribution throughout gestational age. Moreover, recent data show that the diagnostic accuracy of prenatal MRI before 24 weeks of gestation is only slightly inferior to that of MRIs acquired after 24 weeks of gestation (92.4% vs. 94%).<sup>26</sup>

Third, the four groups of fetal MRIs based on residual interhemispheric commissures did not produce significant results. A larger sample is needed to establish a possible prognostic value.

## Conclusions

This study was performed to collect data for prenatal counseling when isolated ACC is detected at fetal MRI, and not to assess the sensitivity of fetal MRI in the diagnosis. We wanted to explore the role of a prenatal MRI-based diagnosis of isolated cACC on the future neurocognitive prognosis, based on long-term follow-up data.

Our results support the view that these children may present with different degrees of impairment becoming more evident only in their second decade of life, namely neurologic and neuropsychological impairments such as deficits in executive and linguistic functions, and learning disabilities. The same holds for behavioral difficulties including deficits in social communication or interaction, or in emotional or social control, inhibition, and hyperactivity.

Postnatal MRI and detailed genetic analysis may add crucial complementary information to prenatal data and substantially influence the final judgment on the outcome and orient clinical management.

## Acknowledgments

The authors are grateful to patients and their parents for their kind cooperation. The work was supported by funds from the Italian Ministry of Health, grant # RC2020 and RC021 (to MTB), grant# RC2020 and RC 2021 (to RB), 5X MILLE and RC 2019 (to RR), and funds from the Fondazione Regionale Lombarda per la Ricerca Biomedica (FRRB) grant # Care4NeuroRare (to MTB).

## Author Contributions

Dr Romaniello was responsible for data acquisition and funding, and manuscript drafting. Dr Arrigoni performed the postnatal neuroradiological study and was involved in revising critically the manuscript. Dr De Salvo performed psychological and neuropsychological study. Dr Bonaglia and Dr Panzeri performed the molecular study and were involved in revising critically the manuscript. Dr Bassi was involved in revising critically the manuscript and acquisition of funding. Dr Parazzini and Dr Righini performed the prenatal neuroradiological study and were involved in revising critically the manuscript. Prof. Borgatti was involved in revising critically the manuscript and in the acquisition of funding. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Conflict of Interest

The authors declare no conflict of interest.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Pre-postnatal MRI concordance.

**Table S2.** Developmental Milestones of the cohort of 50 cACC subjects.

**Table S3.** Rehabilitation program for the cohort of 50 cACC subjects.

**Table 4SA.** Correlation between fetal MR imaging and neuropsychological skills.

**Table 4SB.** Correlation between postnatal MR imaging and neuropsychological skills.

**Figure S1.** Two examples of subjects changing group between fetal and postnatal MR imaging Figure 2S. Additional findings detected at postnatal MRI.