



## Neurodevelopmental outcome in prenatally diagnosed isolated agenesis of the corpus callosum



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### ABSTRACT

Neurodevelopmental outcome in children with agenesis of the corpus callosum (ACC) is correlated with the presence or absence of associated brain abnormalities. Indeed, neurodevelopmental outcome shows severe disabilities when the ACC is not isolated whereas in isolated forms, the neurologic development is mainly normal. Contrary to data in several published studies, the prognosis remains uncertain even in isolated forms, which may lead in France to medical termination of pregnancy.

**Objective:** To evaluate long-term neurodevelopmental outcome in children with prenatally diagnosed isolated ACC.

**Design, setting and participants.**

This is a follow-up study conducted in Normandy (France). It included a cohort of 25 children born between January 1991 and June 2016, with a prenatal diagnosis of isolated ACC and who were followed for at least two years.

**Results:** The average follow-up was  $8 \pm 5$  years. ACC was complete in 17 patients (68%), partial in 5 (20%) and hypoplastic in 3 (12%). Whereas global motor development was normal in each case, normal neurodevelopmental outcome or mild disabilities occurred in 88% children and moderate/severe neuro-disabilities were present in 12% of children. Wechsler Intelligence Scale for Children-IV evaluations and Intellectual Total Quotients were within normal range, but we observed lower scores in verbal comprehension, social judgment, executive functions. A lower score in morphosyntax was observed among 52% of children with oral language disorders.

**Conclusions:** Neurodevelopmental outcome was favorable in most of our patients with isolated ACC, but mild learning disabilities emerged in older children. Long-term follow-up until school age is essential to provide early diagnosis and appropriate care support.

### 1. Introduction

The corpus callosum is the main cerebral commissure connecting the two cerebral hemispheres. Its role is essential in the development and maintenance of hemispheric specialization, including language in the left hemisphere, or face processing, emotion and spatial attention in the right hemisphere. It enables the transfer of inter-hemispheric information. Agenesis of the corpus callosum (ACC) is one of the most common brain defects, with an estimated prevalence of 1 in 4000–5000 in the general population [1]. These figures underestimate the true

incidence of ACC because of a proportion of asymptomatic patients not diagnosed prenatally. ACC may be discovered fortuitously when computed tomography or magnetic resonance imaging (MRI) is performed post-natally for various reasons. ACC can be complete with no corpus callosum at all, resulting from an abnormality of embryogenesis, or partial resulting from abnormal development or subsequent to interrupting events during pregnancy.

ACC is diagnosed prenatally by routine ultrasound at a mean gestational age of 22 weeks. Fetal MRI can be performed during the third trimester to search for associated cerebral abnormalities, as neuronal

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migration or gyration disorders. Several studies have shown poor prognosis in cases of associated ACC and more favorable prognosis for isolated ACC [2–4]. Given the severe neurological prognosis, medical termination of pregnancy may be considered when ACC is associated with brain abnormalities or extra-cerebral birth defects, genetic defects (trisomy 13 or 18), inborn errors of metabolism, as pyruvate dehydrogenase deficiency, fetal alcohol syndrome, or infectious diseases, as maternal rubella and congenital toxoplasmosis. However, termination of pregnancy in cases of prenatally diagnosed isolated ACC is not consensual, as several studies have observed that the neurological prognosis remains uncertain, with a short-term favorable outcome in most patients.

This study was designed to evaluate long-term neurodevelopmental outcome in children with prenatally diagnosed isolated ACC.

## 2. Patients and methods

### 2.1. Patients

We retrospectively reviewed the medical charts of 25 children born between January 1991 and June 2016 in Normandy, France, with a prenatal diagnosis of isolated ACC. Patients with an antenatal diagnosis of apparently isolated Complete ACC (CACC), Partial ACC (PACC), or Hypoplasia of the Corpus Callosum (HCC) were included in the study. The ACC was considered to be isolated antenatally when the fetal karyotype was normal and when no brain abnormalities or extra-cerebral malformations were associated [5]. Presence of interhemispheric cyst (IHC) was not an exclusion criterion. Exclusion criteria consisted of presence of prenatal exposure to alcohol, parental consanguinity and patients with ventricular dilatation, defined as lateral ventricular width > 20 mm [6]. Children under 2 years old and children who were lost to follow-up under the age of 6 years old were excluded. The first results of this study, involving patients born between 1991 and 2003, were published previously and follow-up was continued. The local ethics committee has given its approval for this study. The children were registered in the perinatal network of Eastern Normandy after signed parental consent.

### 2.2. Data

For each patient, we recorded the following data: gestational age at diagnosis, MRI data before and after birth reviewed by an expert radiologist (Dr. M. Brasseur-Daudry), gestational age at birth and clinical examination at birth (weight, size and head circumference). All children were evaluated at 5–6 weeks of age, 6 months old and then annually by a pediatrician or neuropediatrician until the age of 16 years. At each pediatric consultation, the following data were collected: measurements (including head circumference), developmental milestones, cognitive or language skills, visual impairments or hearing loss, or specific educational needs, as physical therapy, speech therapy, special education services and school reorientation, and epilepsy.

### 2.3. Evaluations of neurobehavioral outcomes

Neuropsychological evaluations included the Wechsler Intelligence Scale for Children IV (WISC-IV), the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI-III) and the Wechsler Intelligence Scale for Children-III (WISC-III). Neuropsychological tests were performed in children aged 4–16 years. Children under 4 years old did not take any tests because of their young age. Full-Scale Intellectual Quotient (FSIQ) was considered to be in the middle range if it was between 85 and 115 (68%) and in the lower range if it was between 70 and 85 (13.5%). Mental retardation was defined as an FSIQ below 70 (2.5%).

Neuropsychological tests such as the WPPSI-III or WISC-IV were divided into four sections: verbal understanding including vocabulary, similarity and comprehension; perceptual reasoning including cubes, concept identifying and matrices; working memory including digit sequence of letters and digit memory; and processing speed including codes and symbols. For all four sections, a score of 10 was considered average; with a lower limit of 8 and an upper limit 12.

When deficits in attention were observed during the neuropsychological tests, children received additional attentional tests and were treated by methylphenidate when they were considered to have a significant ADHD (Attention Deficit Hyperactivity Disorder).

Based on the results of these cognitive and motor ability tests, patients were classified into three categories: normal outcome, mild disabilities and moderate/severe disabilities. Neurodevelopment was considered as normal outcome when no cognitive behavioral or motor impairments in psychomotor milestones was detected at last follow-up and when school level was appropriate for age. Mild disabilities were defined as specific cognitive disorders with an FSIQ score in the normal range either in verbal IQ or performance IQ (between 70 and 85), motor disorders or oral language disorders. We defined moderate/severe disabilities as follows: cerebral palsy according to the criteria of the Surveillance of Cerebral Palsy in Europe (SCPE) network [7]; severe cognitive disorders with an IQ score < 70 or autism spectrum disorders according to the diagnosis of the regional reference center of Normandy.

Information regarding children's schooling was also collected. The results of the evaluation of speech therapy assessments were analyzed. A computer based assessment of oral French language before or after the writing stage was performed for children with speech language disabilities ("Bilan Informatisé du Langage Oral": BILO II and III) [8]. The test assessed: lexical decision, oral comprehension, lexical judgment, grammatical judgment, word repetition, lexicon production and morphosyntax.

### 2.4. Analysis and statistics

Due to the small number of children included in the study, results were analyzed descriptively.

## 3. Results (Appendix 1)

Between January 1991 and June 2016, 25 children with prenatal apparently isolated ACC were born in Normandy, France. There were 9 girls (36%) and 16 boys (64%). ACC was complete in 17 (68%), partial in 5 (20%) and 3 children (12%) had HCC. Three children had prenatal diagnosis of IHC: two with CACC (cases #14 and #19) and one with PACC (case #22). ACC was diagnosed prenatally by ultrasound at an average gestational age of 27 (22–34) weeks of gestation (WG). The diagnosis of isolated ACC was confirmed by cerebral MRI during the third trimester of pregnancy for 24 patients showing no additional malformations or clastic lesions.

Amniocentesis was performed for all patients and all standard fetal karyotypes were normal. Cerebral MRI was performed antenatally in 24 patients (96%) and postnatally in 12 (48%) at an average age of eleven months. All patients had at least one cerebral MRI examination in their follow-up (antenatally or postnatally). In two children, postnatal MRI showed previously missed brain abnormalities: asymmetry of the ventricles with a dilated right temporal horn (case #7) and a heterotopy next to the left temporal horn (case #22).

Birth weight was normal for age in all, except for two children who were small for gestational age (cases #1 and #16). Head circumference ranged from – 1.5 to + 3 standard deviations. Physical examinations at birth were normal in 20 children (80%). Dysmorphic features were

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