

Neurodevelopmental outcome in children with a prenatal diagnosis of agenesis of corpus callosum

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ABSTRACT

Introduction. Agenesis of the corpus callosum is the most important change in white matter in the human brain. Absence of this structure can cause delayed motor development, mental retardation, seizures, language, or comprehension difficulties, with the progressive onset of autism, schizophrenia, and attention deficit disorders.

Objectives. Advances in prenatal imaging techniques have led to a significant increase in the detection rate of agenesis of corpus callosum or associate anomalies – cranial and extracranial. Through this, we can advise parents earlier and check over time the development of affected children.

Materials and methods. We studied 23 cases of agenesis of corpus callosum, from which 15 of the women with this fetal diagnosis chose to give birth to 15 live newborns with this pathology, and we started to do follow up on the neurodevelopmental outcome of this children.

Results. The outcome of neurological development for people with corpus callosum abnormalities is highly variable and there is often an overlap in neuropsychological performance between patients with complete agenesis and those with partial agenesis of corpus callosum. The 15 children evaluated showed a diverse evolution from normal to severe, with neuro-psychological regression found and proven over time.

Conclusions. Given the unexpected shift from normal neurological, motor and cognitive functions to borderline and even severe ones, prenatal counseling regarding the prognosis of this disease is difficult.

Keywords: agenesis of corpus callosum, outcome, malformation, neurodevelopmental evolution

INTRODUCTION

The corpus callosum is an extremely important white matter structure, with major consequences in neurodevelopmental outcome and social skills of individuals.

New late imaging techniques such as neurosonography and antenatal MRI have led to a huge detection rate of the agenesis of the corpus callosum (ACC) (Figure 1).

The diagnosis can be certain and accurate at about 20th week of gestation (Figure 2) and it should provide the pregnant woman and the involved couple the best information about the nature of the abnormality and the possible clinical outcome.

The most common symptoms of agenesis of corpus callosum are being represented by the delay in cognitive and motor functions, social and language deficits or epilepsy. Nevertheless, this pathology has been linked to attention deficits disorders, autism, and schizophrenia.

However, the extent of the outcome is influenced by multiple factors – type of agenesis – complete or partial, damaged part of the corpus callosum, associated defects of the child and maybe most reliable – the residual interhemispheric transfer through other commissures (anterior, posterior, or hippocampal) (1,2).

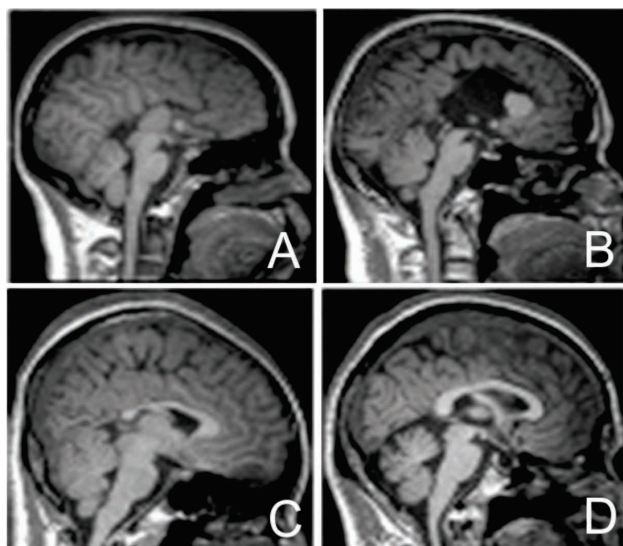


FIGURE 1. MRI Images in sagittal plane of the corpus callosum, with a diagnosis of ACC made by ultrasound, at 23 weeks of gestation. A. Complete agenesis of corpus callosum. B. Partial agenesis of corpus callosum. C. Hypoplasia, a very thin corpus callosum. D. Normal development of the corpus callosum



FIGURE 2. Tomography ultrasound imaging of the brain in axial plane showing mild ventriculomegaly (colpocephaly) and the absence of cavum septum pellucidum at a 23 weeks of gestation fetus (indirect signs of agenesis of corpus callosum)

OBJECTIVES

The study aims to help in training specialists in early agenesis of corpus callosum diagnostic maneuvers and in highlighting the connection between total or partial agenesis and neuro-social development of the newborn and future child.

We tried to develop an early diagnosis system so that parents can be properly and earlier counseled to have more time to decide. Later, we organize a follow-up examination for children whose parents chose to continue pregnancy after receiving clear information concerning the absence of the corpus callosum.

MATERIAL AND METHODS

The study began by gathering useful information about agenesis of the corpus callosum, citing important sources worldwide.

To achieve the proposed objectives, we opted for a prospective, multicentric study.

We enrolled a group of 1,074 pregnant patients with single or multiple pregnancy who were admitted in two obstetrics-gynecology clinics (one private, Polisano Clinic, in Bucharest, and a state-owned, “Prof. Dr. Panait Sîrbu” Hospital, in Bucharest), between 2014 and 2016, for first and second trimester ultrasound. All patients agreed upon the informed consent for the ultrasound and further clinical studies.

Enrollment in the study, both in terms of patient origin as well as admission in the study group, was made on a random basis, which confers representativeness to our results. The Ethics Committee agreement was obtained from both clinics.

We used IBM® SPSS Statistics ver. 20 to implement the descriptive statistics of the specific indicators of our study (frequencies, central tendency, and dispersion indicators), then we applied specific comparison tests, correlation analysis and linear regression in stratified batches, with variables of interest considered; the result interpretation was accepted at p-value below 0.05.

Valid admission criteria were direct and indirect signs of ACC on ultrasound: colpocephaly (typical shape of lateral ventricles - tear drop), separated anterior horns of lateral ventricles, absence of cavum septum pellucidum, ascension of the third ventricle, radial disposition of gyri, abnormal development/absence of pericallosal artery.

Exclusion criteria consisted in pregnant women not willing to sign the consent, those who did not meet the ultrasound aspects mentioned above.

We found 23 cases of ACC, from which 15 of the women with this fetal diagnosis chose to give birth to 15 newborns with this pathology, and we followed up with neurodevelopmental evaluation of this children.

Therefore, our study encompassed 15 newborn investigated since first trimester. We performed measurement of the midbrain and falx cerebri diameters between their 11th and 14th week of gestation, to predict the possibility of the agenesis of the corpus callosum (3,4).

Along with these measurements, we performed the described ultrasound exams, antenatal MRI, chromosomal microarray, and whole exome sequencing looking for direct and indirect signs of the defect (5,6).

The children neuro-psychological evaluation consisted in annual MRI, intellectual quotient measurement using special protocols and scales for pre-

school children (Brunet Lezine, Wechsler, Dellatolas or KABC subtests) (1). We considered a normal range of IQ to be those with a result of over 90.

Considering the results observed by D'Antonio et al. (1), evaluation of these children from a neurodevelopmental point of view, was divided into 3 different categories – normal, borderline, and severe outcome.

RESULTS

Our study includes 15 children born with ACC (agenesis of corpus callosum), of which - 11 cases of complete ACC, 3 cases of partial ACC and one case of hypoplasia.

Evaluation parameters included: visual defects, hypotonia, abnormal coordination, speaking disorders, affected motor control, seizures, epilepsy, and cognitive status (5).

Children in our study were between 12 and 70 months old, of which 9 had normal development, 3 had borderline development, and lastly 3 had severe outcome.

The normal individuals (table 1) did not have associated cerebral disorders, with one exception – a case of interhemispheric cyst seen on ultrasound and confirmed to be Probst bundles replacing the lacking ones.

TABLE 1. Diagnosis and normal evolution

ID	Diagnosis	Test	Pregnancy associated diseases	Associated ACC defects	Gestational week of diagnosis
N1	ACC	US, MRI	blood	AS. Extra cerebral Renal	24,0
N2	Partial ACC	US	drugs	-	23,6
N3	ACC	US	-	AS. SNC	22,4
N4	ACC	US	-	AS. Extra cerebral Cardiac	22,6
N5	ACC	US	-	AS. Extra cerebral Genital	23,1
N6	ACC	US	psychiatric	AS. Extra cerebral Cardiac	24,5
N7	Hypoplasia	MRI	psychiatric	-	24,0
N8	ACC	US	drugs	-	22,1
N9	Partial ACC	US	-	-	23,0

The normal newborns were between 12 and 47 months old now, males and females.

All criteria – motor control, cognitive status, visual sense, coordination and language – are typical for a normal outcome with an intellectual quotient of 90 to 109.

All children had fewer seizures without any epileptic signs observed until now.

The 22 months old girl with hypoplasia cannot be considered to have a superior neurological developmental progress by now.

The prenatal diagnosis of these subjects was obtained between 22 and 24 weeks of gestation by ultrasound and MRI, their mothers had psychological disorders, blood diseases or even drug addictions. Some of these children had associated malformations, as it is shown in table 1.

As for severe outcome (table 2), all criteria include children with a critical evolution, mental retardation, and an IQ below 69.

All girl patients had severe complications – septo-optic dysplasia or Dandy Walker malformation, with one exception – one girl with no associated pathology at birth nor mother's pregnancy complications (table 2). This case was prenatally diagnosed with complete ACC, is currently 70 months old (the oldest child in our study) and her condition has not observed any changes since her initial evaluation.

TABLE 2. Diagnosis and severe evolution

ID	Diagnosis	Test	Pregnancy associated diseases	Associated ACC defects	Gestational week of diagnosis
SO1	ACC	MRI	+	AS. cerebral	21,0
SO2	ACC	US	-	-	24,0
SO3	ACC	MRI	+	As Extra cerebral-bone	22,0

All children have developed epilepsy, with no fine motor control, difficulties swallowing, they are unable to speak properly and need special assistance.

In the borderline group (table 3) we had one child with postaxial polydactyly and ventricular sept defect – VSD (table 3) that was included in this group since birth.

TABLE 3. Diagnosis and borderline evolution

ID	Diagnosis	Test	Pregnancy associated diseases	Associated ACC defects	Gestational week of diagnosis
B1	ACC	US, MRI	-	AS. Extra cerebral Cardiac polydactyly	22,4
B2	ACC	US	Infectious disease	-	23,1
B3	Partial ACC	US	Infectious disease	-	23,0

The other two children with complete ACC were included first in the normal group with progressive degradation of cognitive functions as they grew older. They had sudden slowing in the neurodevelop-

mental status between the 24th and 32nd month of life.

Subjects are under regular examination (MRI, neurologic, psychologic, and psychiatric evaluation scales – Brunet Lezine, McCarty, Wechsler), for ongoing development of their condition.

DISCUSSIONS

Newborn and children were further investigated by psychometric scales by pediatric neurologists, psychologists, and psychiatrists

Sotiriadis and Makrydimas, in their study in 2011 (7), consider a percentage of approximately 65-74% children to have a normal development in case of an isolated ACC, next to an 8% for disability, borderline or severe. Affected patients usually have seizures (40%), mental retardation (80%), vision or hearing defects, learning delay, different hygiene or eating habits, behavior harmful to themselves (8). As we see, our results are similar – with 9 of 15 (~60%) children with normal behaviour while 20% of children showed extremely modified development (8,9).

It is important to understand that the outcome of prenatally detected ACC is mainly dependent on the associated anomalies or their absence, as other studies (9), including the current one, point out. Proper counselling for isolated ACC will lower rate of pregnancy termination (10), given the fact that isolated ACC is considered a benign finding, particularly in male fetuses (11).

As we try to lower the gestational age of diagnosis by ultrasound, neurosonography, MRI and even karyotyping, we should be able to give better advice to parents (10).

The outcome of postnatal diagnosed ACC is always worse, compared to the prenatally diagnosed disease, because of patients seeking medical care due to onset of symptoms (11-14).

Limitations

ACC is a very little-known disease, and rarely diagnosed properly. Clear staging of children development (normal versus borderline) is best attempted during middle school education. Since cognitive function depreciation occurs over a longer period, leading to few long-term studies, we believe our study is a step in the right direction.

Considering existing follow up loss rate on patients in Romania, we will need more studies to define a more precise age where developmental changes take place.

CONCLUSIONS

It is mandatory to understand that age is a major criterion for evolution placement, with progressive shifting of IQ to a lower range. A normal IQ can hide real deficiencies in social skills, coping with stress, language impairment, these details become clear at school age and later in life.

Pre-school patients cannot be accurately evaluated, subtle difficulties and delays are observed after they reach 4 years of age.

Normal development is not guaranteed in cases of isolated agenesis of corpus callosum, however associated pathologies (cardiac, genital, renal, cerebral or bone malformations) will always worsen the outcome.

Prenatal counselling remains very difficult as giving precise information on outcome is very challenging.

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REFERENCES

1. D'Antonio F, Pagani G, Familiari A, Khalil A, Sagies TL, Malinger G, Leibovitz Z, et al. Outcomes Associated With Isolated Agenesis of the Corpus Callosum: A Meta-analysis. *Pediatrics*. 2016 Sep;138(3):e20160445.
2. Mangione R, Fries N, Godard P, Capron C, Mirlesse V, Lacombe D, Duyme M. Neurodevelopmental outcome following prenatal diagnosis of an isolated anomaly of the corpus callosum. *Ultrasound Obstet Gynecol*. 2011 Mar;37(3):290-5.
3. Lachmann R, Sodre D, Barmpas M, Akolekar R, Nicolaides KH. Midbrain and falx in fetuses with absent corpus callosum at 11-13 weeks. *Fetal Diagnosis and Therapy*. 2013;33(1):41-6.
4. Nica E, Mitran M, Marinescu B. Early sonographic signs in agenesis of fetal corpus callosum. *Ginecologiaro*. 2020;8(30):8-11.
5. Volpe P, Paladini D, Resta M, Stanziano A, Salvatore M, Quarantelli M, et al. Characteristics, associations and outcome of partial agenesis of the corpus callosum in the fetus. *Ultrasound in Obstetrics & Gynecology*. 2006;27(5):509-16.
6. Chadie A, Radi S, Trestard L, Charollais A, Eurin D, Verspyck E, et al. Neurodevelopmental outcome in prenatally diagnosed isolated agenesis of the corpus callosum. *Acta Paediatrica*. 2008;97(4):420-4.
7. Sotiriadis A, Makrydimas G. Neurodevelopment after prenatal diagnosis of isolated agenesis of the corpus callosum: an integrative review. *American Journal of Obstetrics And Gynecology*. 2012; 206(4):337 e1-5.
8. Doherty D, Tu S, Schilmoeller K, Schilmoeller G. Health-related issues in individuals with agenesis of the corpus callosum. *Child Care Health Dev*. 2006;32(3):333-42.
9. Goodyear PW, Bannister CM, Russell S, Rimmer S. Outcome in prenatally diagnosed fetal agenesis of the corpus callosum. *Fetal Diagnosis and Therapy*. 2001;16(3):139-45.

10. Sileo FG, Di Mascio D, Rizzo G, Caulo M, Manganaro L, Bertucci E, et al. Role of prenatal magnetic resonance imaging in fetuses with isolated agenesis of corpus callosum in the era of fetal neurosonography: A systematic review and meta-analysis. *Acta Obstet Gynecol Scand.* 2021;100(1):7-16.
11. Bayram AK, Kutuk MS, Doganay S, Ozgun MT, Gumus H, Basbug M, et al. An analysis of 109 fetuses with prenatal diagnosis of complete agenesis of corpus callosum. *Neural Sci.* 2020;41(6):1521-9.
12. Kim SE, Jang HI, Chang KH, Sung JH, Lee J, Lee J, et al. Clinical outcomes and neurodevelopmental outcome of prenatally diagnosed agenesis of corpus callosum in single center of Korea. *Obstet Gynecol Sci.* 2017;60(1):8-17.
13. Raile V, Herz NA, Promnitz G, Schneider J, Tietze A, Kaindl AM. Clinical Outcome of Children With Corpus Callosum Agenesis. *Pediatr Neurol.* 2020;112:47-52.
14. Vergani P, Ghidini A, Strobelt N, Locatelli A, Mariani S, Bertalero C, Cavallone M. Prognostic indicators in the prenatal diagnosis of agenesis of corpus callosum. *Am J Obstet Gynecol.* 1994 Mar;170(3):753-8.