Agenesis of corpus callosum: genetics, epidemiology and neuroimaging findings

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ABSTRACT

Agenesis of the corpus callosum (ACC), a failure to develop the large bundle of fibres that connect the cerebral hemispheres, occurs in 1:4000 individuals. It is characterized by a partial or complete absence (agenesis) of an area of the brain that connects the two cerebral hemispheres. The cause of ACC is usually not known, but it can be inherited as either an autosomal recessive trait or an X-linked dominant trait. It can also be caused by an infection or injury during the twelfth to the twenty-second week of pregnancy leading to developmental disturbance of the fetal brain. Intrauterine exposure to alcohol can also result in ACC. In some cases mental retardation may result, but intelligence may be only mildly impaired and subtle psychosocial symptoms may be present. Prognosis varies depending on the type of callosal abnormality and associated conditions or syndromes. Online searches of the databases EMBASE, PubMed, and Medline were performed, using the search terms children, corpus callosum, agenesis, absence, genetics, and neuroimaging. In this article, we presented genetics, epidemiology, and neuro-imaging of ACC for the last decade

Key words: corpus callosum, agenesis, children

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INTRODUCTION

Agenesis the corpus callosum (ACC) designates a group of malformations that range in severity from minor degrees of deficiency of the splenium to total failure of formation of the telencephalic commissunes [1,2].

The corpus callosum is the main transverse tract of fibers that connects the two cerebral hemispheres [3]. It is made of more than 200 million nerve fibers. The primary function of the corpus callosum is to integrate motor, sensory, and cognitive activity between the left and right hemispheres. The corpus callosum develops during the 12 - 16th week of fetal gestation [3]. Once formed, the callosum thickens with increasing myelination, except during a period of axonal elimination near birth. Postnatally the corpus callosum undergoes a burst of growth during the first four years of life. By the time a child is approximately 12 years of age, the corpus callosum functions essentially as it will in adulthood, allowing rapid interhemispheric interaction.

Although the corpus callosum is not the only path connecting the hemispheres, it is by far the largest and most important [3]. Other interhemispheric connections include the anterior commissure which is about 50,000 fibers, as well as the posterior commissure and the hippocampal commissure, both of which are smaller even than the anterior commissure [3]. Often individuals with ACC have some other much smaller inter-hemispheric connections (i.e. the anterior commissure) [3]. While this may allow for some information transfer between the hemispheres, no other commissure has the same functionality as the corpus callosum. If the corpus callosum does not form prior to birth, it will never form. If there are some corpus callosum nerves crossing between the hemispheres at birth, these may continue to develop but new fibers or nerves won't develop. Since ACC is congenital (occurs before birth), all the rests of the brain connections are organized accordingly [3]. ACC is one of the most prevalent brain malformations [4], and it is seen in many syndromes of various etiologies [5]. Although ACC is predominantly genetic, few genes have as yet been identified.

Genetics

O'Driscoll et al. [5] constructed and analyzed a comprehensive map of ACC loci across the human genome using data generated from 374 patients with ACC and structural chromosome rearrangements. They identified 12 genomic loci that are consistently associated with ACC, and at least 30 other recurrent loci. In addition, these data supported the hypothesis that many ACC loci confer susceptibility to other brain malformations as well as ACC, such as cerebellar hypoplasia, microcephaly, and polymicrogyria.

Backx et al. [6] identified a male patient presenting with intellectual disability and ACC, carrying an apparently balanced, reciprocal, de novo translocation t(6;14)(q25.3;q13.2).

Filges et al. [7] reported on the clinical and molecular cytogenetic findings in a girl with ACC, epilepsy and developmental delay. A de novo 5.45 Mb deletion almost exclusively located within 1q42 was found to cause this phenotype, which shows significant overlap with the microdeletion 1q41q42 syndrome reported in a few patients except for ACC. They suggested that an interaction of genes involved in pathways of embryonic development rather than haplo insufficiency of single genes in the so-called critical regions is causing complex malformation syndromes due to cytogenetic microaberrations in the 1q4 region.

Sailn-Cantegrel et al. [8] examined missense and protein-truncating mutations of the human potassium-chloride co-transporter 3 gene (KCC3) cause hereditary motor and sensory neuropathy with ACC, which is a severe neurodegenerative disease characterized by axonal dysfunction and neurodevelopmental defects. They reported a novel and more distal HMSN/ACC-truncating mutation (3402C→T; R1134X) that eliminates only the last 17 residues of the protein.

Epidemiology

Data regarding the epidemiology of callosal anomalies are contradictory. ACC incidence varies as a function of both diagnostic techniques and sample populations: in the general population, its estimated prevalence is 3-7 per 1000 birth, while in children with developmental disabilities it is 2-3 per 100 [9,10].

In American study using a large population-based registry of birth defects, Glass et al. [10] ascertained 630 cases of ACC and hypoplasia (HCC) of the corpus callosum diagnosed in the first year of life among 3.4 million live births from 1983 to 2003. Multivariable Poisson regression analysis was used to examine demographic risk factors. The combined prevalence of ACC and HCC was 1.8 per 10,000 live births. Fifty-two percent of cases were male. Infants with ACC had an almost fourfold higher prevalence among infants born prematurely when compared with children born > or =37 weeks gestation. After adjusting for paternal age, advanced maternal age

>/=40 year was associated with ACC in infants with a chromosomal disorder.

Szabó et al [11] performed a population-based retrospective survey to study the birth prevalence and clinical features of ACC or HCC and accompanying central nervous system (CNS) and somatic abnormalities in southeastern Hungary between July 1, 1992 and June 30, 2006. Among 185,486 live births, 38 patients (26 boys and 12 girls) manifested ACC or HCC, corresponding to a prevalence of 2.05 per 10,000 live births.

Neuroimaging diagnosis ACC

The diagnosis of callosal agenesis depends on neuroimaging [12-16]. In the newborn, before closure of the anterior fontanelle occurs, screening ultrasonography may clearly show ACC; it may also show parallel lateral ventricles, interhemispheric cysts, hydrocephalus, and other related anomalies. Ultrasonography was the first imaging modality to allow direct sagittal imaging of callosal dysgenesis [15,16] and can identify ACC in the second trimester of pregnancy (18-20 weeks gestation) [17].

ACC is often associated with other anomalies such as Chiari II malformation with abnormal development of cerebellar vermis and medulla oblongata, which tend to descend into the foramen magnum, usually accompanied by myelomeningocele, basilar type encephalocele and disorders of neural migration (which occurs concurrently in human brain development) such as schizencephaly, lissencephaly, pachygyria, marked neuronal heterotopias [13,14,16].

Diagnosis of ACC is sometimes difficult. The characteristic signs suggestive of ACC are: moderate distension of the occipital ventricle and the ventricular communications; absence of the spectrum giving rise to an upward displacement of the third ventricle shown in the anterior coronal section (especially in transvaginal ultrasonography); radial position of the fissures on the internal side of the cerebral hemisphere seen on the sagittal section; the absence in color coded Doppler of the pericallosal artery normally characterized by a semicircular vessel observable on the median sagittal section. At present, color coded Doppler should give the diagnosis of ACC. The developpment of 3D echographic imaging should allow an even more sophisticated approach to this diagnosis giving even more precise prognosis [17].

Magnetic resonance imaging (MRI) is currently the imaging procedure of choice in infants and children with ACC, even in patients who have previously undergone CT and ultrasonography examinations. The multiplanar capability and high soft-tissue contrast that are possible with MRI permit confident diagnosis of ACC and its associated anomalies, especially neuronal migration anomalies or atypical forms of holoprosencephaly [18-20].

Recent MRI findings [18] suggest that ACC might lie along a dysgenetic spectrum, including all commissural anomalies as part of an overall cerebral dysgenesis. Abnormal sulcation is common and suggests more diffuse white matter dysgenesis in these fetuses [19], even if some authors do not consider this as an additional brain abnormality [20].

The fusion of Diffusion MRI and Functional MRI give better visualization and diagnosis of the ACC and HCC [3].

Manfredi et al. [21] evaluated the role of MRI in the diagnosis of ACC - isolated or associated with other anomalies - in fetuses with mild cerebral ventriculomegaly, as depicted at prenatal sonography. Quantitative image analysis included the size of the transverse diameter of the lateral ventricles, in the axial plane, and the thickness of the adjacent cerebral cortex. Qualitative image analysis included morphology of the lateral ventricles, signal intensity changes of the fetal brain, interruption of the germinative matrix, agenesis of the corpus callosum (complete or partial) and associated malformations. Mean axial diameter of the lateral ventricle was 11.6 mm (range 10-15 mm), and mean thickness of the adjacent cerebral cortex was 2.1 mm (range 1.8-3 mm); 23/33 fetuses (70%) showed normal morphology of the lateral ventricles, and 8/33 (24%) showed abnormal morphology (parallel pattern, colpocephaly). The entire corpus callosum was visualized in 20/33 fetuses (60%). In 8/33 fetuses (25%), partial agenesis was diagnosed, whereas in 5/33 (15%), there was hypogenesis. In 6/13 fetuses (46%), isolated ACC was detected, and two cases of hypogenesis of the corpus callosum were misinterpreted - overestimated in one case and underestimated in another.

Diffusion tensor imaging (DTI) in combination with 3D-tractography reconstructions allows studying the neuro-architecture of complex brain malformations in vivo [22]. Prenatal, in utero DTI has been limited by long acquisition times, poor signal to noise ratio and multiple artifacts. Recent developments in hard- and software allow collection of high-quality DTI data sets in utero. Moeded et al. [22] reported on the DTI and tractography data of a fetus with a ACC. They showed that the neuro-architecture of the fetal brain can be studied in excellent detail.

Clinics

ACC [21] may occur as an isolated malformation or as a component of more complex malformation syndromes. It has been associated

with several consistent chromosomal rearrange-ments in more than 20 autosomal and X-linked malformation syndromes. This extreme genetic heterogeneity may be due to the embryologic processes underlying the formation of the corpus callosum. No single gene has been proven to be implied in all patients with ACC [23,24].

Environmental factors are relevant as well: this is evidenced by the effect of ethanol on corpus callosum development, so that ACC is a relatively common feature of Fetal Alcohol Syndrome [25].

ACC has been associated with a number of neuropsychiatric disorders, from subtle neuro-psychological deficits to Pervasive Developmental Disorders [26]. Etiology and pathogenetic mechanisms have been better understood in recent years, due to the availability of more adequate animal models and the relevant progresses in developmental neurosciences.

ACC is an anomaly that may occur as isolated or in association with other central nervous systems or systemic malformations. Popa et al. [27] reported the case of an infant antenatal diagnosed with ventriculomegaly referred in the postnatal period to our department for imaging evaluation. Ultrasonography showed the absence of the corpus callosum and an interhemispheric lesion highly suggestive for a cerebral lipoma. The diagnosis was confirmed through MRI.

Among 38 patients (26 boys and 12 girls) callosal anomalies were isolated in 18 patients, and were associated with other central nervous system malformations in five children [11]. Both the CNS and noncentral nervous system abnormalities were evident in seven patients, whereas callosal dysgenesis was accompanied only by somatic anomalies in eight children. Five of 18 patients with isolated ACC/HCC remained asymptomatic. Developmental delay, intellectual disability, or epilepsy occurred in all patients, except one, when callosal anomalies were combined with other brains or somatic abnormalities. Five patients with multiplex malformations died. Callosal anomalies form a clinically significant and relatively frequent group of central nervous system malformations.

Callosal anomalies were often seen in the context of a chromosomal abnormality (17.3%) and with accompanying somatic (musculoskeletal 33.5% and cardiac 27.6%) and brain malformations (49.5%) [10]. Callosal anomalies form a clinically significant and relatively frequent group of malformations of the CNS that are associated with increased risk of premature birth, are more common with advanced maternal age and are frequently part of a complex, multisystem disorder.

Lemka et al. [28] evaluated thirty children aged four months -15 years with ACC treated in clinics of the Medical University of Gdansk. The clinical signs and symptoms in an isolated ACC and in ACC with accompanying other cerebral malformations were analysed. In 13 children (43%) ACC was an isolated CNS malformation, in 17 patients (57%) other the CNS abnormalities have been found. In some of the children, ACC coexisted with the lesions of other organs. In one girl Apert syndrome, in one boy - Toriello-Carev syndrome, in another boy die VATER sequence were diagnosed. In three females clinical signs were typical of Aicardi syndrome. In one case of newborn congenital cytomegalovirus infection has been established, in one male infant the ring chromosome, in another child the microdeletion of chromosome 22 were diagnosed.

Previous studies have revealed that individuals with ACC have deficits in inter-hemispheric transfer, complex novel problem-solving, and the comprehension of paralinguistic aspects of language. Case studies and family reports also suggest problems in social cognition. Indivi-duals with ACC showed a deficiency in the recognition of emotion, weakness in understanding paradoxical sarcasm, and particular difficulty interpreting textual versus visual social cues [29].

Toriello-Carey syndrome is a rare multiple congenital anomaly syndrome comprising ACC, telecanthus, short palpebral fissures, abnormal ears, Pierre Robin sequence, and cardiac anomaly [30]. Autosomal recessive inheritance has been hypothesized and chromosome abnormalities have been reported.

Booth et al. [31] reviewed and summarized findings from their recent research comparing autism and ACC. They discussed their findings in the context of the "fractionable triad" account and highlight three main points. Firstly, the social aspects of autism can be found in isolation, not accompanied by the nonsocial features of this disorder, supporting a view of autism as a "compound," rather than "monolithic," condition. Secondly, many young people with ACC showed emotion-processing deficits akin to those seen in autism. Diagnostic overshadowing may mean these people do not receive interventions that have proven beneficial in autism.

Conti et al. [32] reported on a patient with ACC, severe mental retardation, infantile spasms and subsequent intractable epilepsy, spastic and dyskinetic quadriparesis, severe limb contractures, and scoliosis. They described phenotype was due to a novel non-conservative missense mutation in the ARX homeodomain (c.1072A>T; p.R358W), inherited from the unaffected mother.

CONCLUSIONS

The cause of ACC is usually not known, but it can be inherited as either an autosomal recessive trait or an X-linked dominant trait. In some cases mental retardation may result, but

intelligence may be only mildly impaired and subtle psychosocial symptoms may be present. Prognosis varies depending on the type of callosal abnormality and associated conditions or syndromes. MRI is currently the imaging procedure of choice in infants and children with ACC, even in patients who have previously undergone CT and ultrasonography examinations.

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