RETRACTED: CORPUS CALLOSUM AGENESIA A MINIREVIEW

ACTA MEDICA MEDITERRANEA journal is retracting this paper following on concerns raised by the Journal Owner, Mister Carmelo Pennino, the manager of Carbone Editore company. After an internal investigation that involved all Section Editors, the journal owner detected a suspected misconduct in terms of self-citations activity. The link of the retracted article http://www.actamedicamediterranea.com/archive/2018/special-issue-4/corpus-callosum-agenesia-a-minireview

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ABSTRACT

The corpus callosum (CC) is the largest of the fiber bundles present in the human brain, and its name derives from its hard consistency caused by the presence of myelinated fibers. It represents the largest and most voluminous brain commissure and a white matter station. CC alterations may be identified in many neurodevelopmental disorders.

Keywords*: corpus callosum, agenesia, cerebral abnormalities.*

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Introduction

The corpus callosum (CC) is the largest of the fiber bundles present in the human brain, and its name derives from its hard consistency caused by the presence of myelinated fibers. It represents the largest and most voluminous brain commissure and a white matter station[(1-7)]. Within the nervous system there are different types of fibers: commessural fibers, projection fibers and associative fibers; the CC is a commessural fiber, that is, it connects the corresponding areas of the two cerebral hemispheres. It is shown as a white plate stretched transversely between the two hemispheres. It contains 300 mil-

lion axons that for the most part connect similar sites in the two hemispheres, but also terminate in areas other than those of which the axons originated. All cortical areas receive commessural fibers, with the exception of the hand area o on the cortex and the area 17. Beyond the limit of the ventricular cavities the fibers of the CC radiate the white substance of the hemispheres to reach the cortex[8-12].

A free surface is distinguished in the CC that is visible at the bottom of the interhemispheric fissure and a part hidden in the thickness of the hemispheres; the latter forms the radiations of the CC. The free part is divided into the trunk and the knee; the trunk of the CC is that part in the form of a quadrilateral lamina which appears at the bottom of the interhemispheric fissure, the knee being formed by the inflection of the anterior extremity of the trunk.

Following it presents other 4 components: the rostrum, knee, body and splenium. The rostrum of the CC forms the floor of the front end of the frontal body and is crossed by horizontal fibers that make up the white commissure of the base and fibers coming from the orbital and inner face of the first frontal convolution. A thin gray laminette, the terminal lamina, it rises from the upper edge of the chiasm to join the rostrum and close the diencephalic wall. The splenium is that part of the CC which later bends and ends in a large thickened margin[13-15].

The fibers of the CC originate from the small and medium pyramidal cells of the bark of a hemisphere and reach the cortex of the other hemisphere. The fibers corresponding to the trunk of the CC come from the posterior portion of the frontal lobe, from the parietal lobe, from the insula, from the supracallose gyrus and from the posterior part of the temporal lobe. The fibers corresponding to the knee radiate in the anterior portion of the frontal lobe; those corresponding to the rostrum instead radiate towards the orbiting gyrations. The splenium fibers behave differently, the upper ones spread in the posterior part of the supracallosum gyrus, in parietal and temporal lobes, those of the extreme edge and the inferior face of the splenium reach the cortex of the occipital lobe and surround the posterior horn of the ventricle.

CC allows the unification of the information processed differently from each hemisphere, realizing the complementarity between the two halves of the cerebral cortex. It is involved in the interhemispheric communication, it provides connections between homologous cortical areas, while the anterior areas of the cortex are connected through several front portions of the CC, for example, anterior orbital, frontal anterior and superior frontal and the same occurs for the posterior area, parietal superior, parietal posterior, temporal and occipital. The callous fibers, referred to previously, constitute connections between cortical areas related to peripheral motor functions and sensory-sensory functions. Physiology shows that auditory, visual and tactile information is processed through the CC and that it intervenes in the coordination of movements and language. The CC is the first stretch of neuronal fiber that connects the two cerebral hemispheres and allows the transfer and integration of motor, sensory and cognitive information[16-20]. Clockwise, we can declare, which is separated into 4 components: rostrum, knee, body and splenium; the bottleneck between the body and the splenium is called the isthmus.

The formation of it depends on a series of highly regulated complex events in the course of development that begin during gestation and continue into adulthood. The rupture of one or more of these events can lead to the agenesis of the CC or a disorder characterized by the complete or partial loss of one or more components of the CC. In the adult the CC has the shape of a half moon and a length of about 10 centimeters (Figure 1).

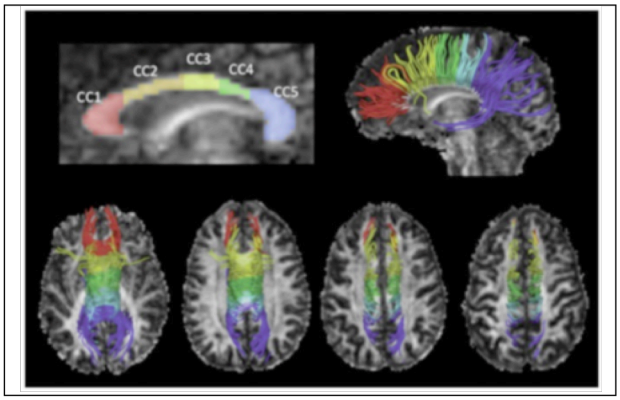

Figure 1: shows the schematic tracrographic anatomy of Corpus Callosum.

Embryogenesis of the CC

The CC appears late in the cerebral ontogeny, between 12 and 18 weeks of gestation. After closing the neural tube, during the fourth week of gestation, the thin rostral wall of the telencephalon extends from the optic chiasm to the transverse veil. Between 6 and 8 weeks of gestation, when the fetus has reached between 15 and 30 mm of CRL (sacred vertex length), there is a rapid increase in thickness in

the final dorsal part of the rostral wall. This thickness represents the lamina reuniens, and as this region develops, the axons of both hemispheres will grow in it. The ventral part remains unchanged and becomes the lamina terminalis that forms the anterior wall of the third ventricle. At 8-9 weeks of gestation, groups of fibers grow medially from the ventrolateral wall of each hemispheric vesicle. At the 10th week the two groups of fibers meet and cross on the median line of the lamina reuniens forming the anterior commissure. During the 8th week of gestation the dorsal part of the lamina reuniens begins to bend in a median scaly called sulcus medianus telencephali medii (SMTM). During the 9th week all the cells of the lamina reuniens migrate into the SMTM which results to be filled with these cell masses. This large cellular mass is the residue of the obliterate sulcus medianus telencephali medii, and is known as the commissural mass.

This develops in the dorsal direction along the SMTM within 5-7 weeks and becomes the bed for the regrowth of the commissural fibers of the CC. Between 11-12 weeks of gestation, the callused pioneer fibers begin to enter the commissural mass. From 12 to 13 weeks the definitive callosum body is formed in the region of the commissural plaque, which will become the knee of the CC. Growth will continue for the next 5-7 weeks in a caudal direction, reflecting the rapid pace of caudal growth of the cerebral hemispheres. The growth of the CC occurs from the front to the back, in fact the knee is formed, then the anterior body, the back body and the splenium. The exception of this order is the development of the rostrum, it is the first to form, between 18-20 weeks of gestation. Although all components of the CC at this point are formed, the structure of the CC is not yet completed. The cortical plates of the hemispheres are enlarged, the axons extend to associate fibers of distant regions of the brain. The majority of them cross towards the lateral hemisphere and this happens through the CC; that thickens and widens. The knee and the splenium become bulbous. This process continues until growth has ceased. So summing up, the formation of the CC begins already at 6 weeks of gestation, when the axons destined to cross the median line can be seen growing medially between the hemispheres.

During embryonic development the anterior commissure develops as a connecting connection between the olfactory regions of the left and right sides. Above it is formed an even larger, voluminous and strongly myelinated commissure: the CC, which joins the corresponding areas of the cerebral cortex of the two sides, and extends in a caudal direction above the arch. At 12-13 weeks of gestation, the first fiber crosses the midline through the commissural mass that is located between the anterior chapping of the hippocampus that form the CC. It has also been found that a large number of cells belonging to the glial population play an important role in the development of the CC. One of these populations the so-called "hinge glia" has been shown to guide the fusion processes of the midline, a necessary event for the formation of the CC; other glial populations identified that contribute to the formation of the CC are the "glia wedge". Another important structure for the CC formation is called "midline sling", which mainly consists of neuronal migration, forms a bridge along the midline where, the axons of the CC, grow to reach the lateral hemisphere. While the development of the anterior commissure, the hippocampal commensure and the splenium cross the lamina reines, the anterior part (which circumscribes the pellucid septum) has its development, processes and crosses through the meninges of the interhemispheric fissures. Given the complexity of the formation of the CC, the causes of the agony of the CC can be multiple and can usually be associated with other conditions[21-26].

Corpus callosum agenesis (ACC)

CC is the first stretch of neuronal fiber present between the two cerebral hemispheres that allows the transfer and integration of sensory and cognitive motor information. It transfers cognitive information of a higher order and plays a particularly important role in carrying out complex tasks, social interaction, language and abstractive reasoning[27-35].

Studies indicate that the corpus callosum is organized topographically so that its anterior region is connected to the anterior section of the brain, while the posterior region of the corpus callosum is connected to the posterior part of the brain. Different types of anomalies concerning the morphological and anatomical structure of the corpus callosum have been identified. They are distinguished in: hypoplasia, the corpus callosum is thinned, on the contrary, hyperplasia the corpus callosum is thickened and agenesis, ie absence of the corpus callosum. Agenesis and hypoplasia indicate, correspondingly, the absence of an organ (agenesis) and an abnormal development of an organ or a tissue (hypoplasia) that may be reduced or incomplete.

ACC is a disorder characterized by complete or partial absence of the components of the corpus callosum; it can be completely absent in individuals, or, they may lack one or more of its components (rostrum, splenius, body, genu). In addition, the CC agenesia appears, albeit rarely, isolated or more frequently associated with other cerebral and extracerebral malformations and genetic syndromes, such as: abnormal neuronal migration, white matter change, Dandy-Walker syndrome and Chiari II[36-52].

It is difficult to estimate exactly the incidence of cases of agenesis of the corpus callosum; the best results available probably come from California Birth Defect Monitoring which suggests a prevalence of about 1.4 per 10000 live births with agenesis of the corpus callosum and 0.4 per 10000 live births with hypoplasia of the corpus callosum. However, these figures may make the incidence appear lower than the real one because probably a percentage of asymptomatic individuals might have escaped during the detection of these data.

The agenesis of the corpus callosum is an extremely heterogeneous condition, which may be the result of the rupture of some important steps during development[36-52].

Several causes have been identified for this condition, although very often, the ACC is a consequence of multifactorial harm. The main causes to which ACC can be attributed are: genetic causes due to the mutation of one or more genes or variation in the number of copies of chromosomes; severe autosomal dominant syndromes, autosomal recessive or X-linked syndromes; congenital infections; metabolic disorders; toxic agents, alcohol abuse during pregnancy, maternal phenylketonuria. In addition the ACC was also observed in some trisomies due to the rearrangement of chromosomes such as chromosome 4 (p16), chromosome 6 (q23), chromosome 8 (p21 p23) and chromosome 11 (q23), suggesting that some genes responsible for the agenesis can be located in these chromosomal regions. More than 30 loci have been identified through the use of CGH-microarray technology in the entire human genome that contain genes that cause the agenesis of the corpus callosum, such as the duplication of chromosome 7q 36.3 involving two genes: RNA Binding Motif Protein 33 (RBM 33) and Sonic Hed gehag (SHH) which is also associated with Chiari malformation. The identification of ACC-causative genes highlighted the wide phenotypic variability of this disorder[36-52].

ACC can often be the result of an asymptomatic clinical manifestation.

Preterm born children and adolescents often present learning difficulties and worse overall cognitive performance that have been associated with the reduction of the corpus callosum[36-42].

In some studies, gestational age has been associated with the measurement of corpus callosum in preterm infants and children. Anderson and al measured the length of the corpus callosum in 64 children born long before the term and established 3 different groups depending on the gestational age: 23 to 25 weeks, 26 to 29 weeks and 30 to 33 weeks. The results were compared with the growth rate of prenatal outcomes. Authors concluded that CC grows at a much lower rate after birth than in utero among very premature infants[53-60].

People born very prematurely (VPT) have a higher risk of presenting brain abnormalities, especially prominent in white matter. Studies have been carried out to find a consistent reduction of the anterior and posterior part of the corpus callosum, especially of the genuine in preterm or very preterm infants. A distinction is made on the basis of weight and gestational age in children born before the end of pregnancy or before the 40th week[53-60].

The World Health Organization (WHO) defines the preterm birth that occurs before the 37th week of gestation (that is, before 259 days from the start date of the last menstrual period).

The preterm infant is defined as Premature for its aspects of structural immaturity, that is, for a non-complete development of the organs and their functions. Its main characteristic consists in the condition itself pathological, not to spend the last months of pregnancy within the womb. Preterm children are classified by weight: Low birth weight 1501-2500 gr, Very low birth

weight <1500 gr, Very low birth weight <1000 gr, Extremely low birth weight <750 gr; or in relation to the gestational age: Appropriate for gestational age 10 -90 percentiles, Small for gestational age <10° P, Large for gestational age> 90. In the corpus callosum, the region extending from the rostrum to the back of the body is predominantly predominantly of fibers that connect the prefrontal cortex. This increases the importance of studies on cognitive functions that are highly dependent on the prefrontal cortex. Preterm born teenagers show severe deficiencies in verbal and oral speech, for the most part part because with regard to other categories the studies carried out report different results[61-70].

Prenatal and postnatal diagnosis

In general brain malformations are the most common fetal anomalies, about one in 100 live births presents abnormalities of the central nervous system, ultrasound and magnetic resonance are the tools of investigation used during pregnancy (43-53).

The complete diagnosis of the corpus callosum is based on the direct results, when the corpus callosum is not visualized, and indirect: lack of visualization of the pellucid cable, upward displacement of the third ventricle, lateral displacement of the lateral ventricles and parallelism of the atria (the lateral ventricles tend to be wider than normal), abnormal formation of the cerebral furrows. Even the Colpocephaly (abnormal appearance of the brain) is commonly observed. The Agenesis of the partial callosum body is suspected when the corpus callosum appears too short. The hypoplastic or hyperplastic corpus callosus is instead suspected when the corpus callosum appears too thin or thickened. It is preferred for the diagnosis to use both the ultrasound and the magnetic resonance imaging to have a more complete visualization of the corpus callosum; precisely because the anterior part of the corpus callosum is usually delineated better via ultrasound while the back is better represented by MRI. Ultrasonography is a medical diagnostic investigation, in this case also prenatal, carried out after 20 week of gestation, which uses ultrasound, the fundamental problem of ultrasound as a diagnostic tool of ACC is that it uses axial scans and is not possible have the direct visualization of the corpus callosum; further transvaginal probes may be used for further investigation when the fetal head is engaged[54-65].

A further investigation when a suspect of ACC is present is carried out by MRI; allows us to receive information other than ultrasound because the images we can obtain come from three different planes: sagittal, axial and coronal. ACC is considered isolated when the prenatal workup that includes MRI and genetic testing reveals no anomaly added. In fact, if the family history is positive for mental retardation, epilepsy, psychiatric disorders, when there is a family or abnormal consanguinity observed during pregnancy as the nuchal anomaly, intrauterine growth retardation, infections, drugs and alcohol intake with reduction of fetal movements is probably genetic, metabolic or infectious disease. Prenatal diagnosis of hypoplasia and partial agenesis may be more difficult than complete Agenesis but it is nevertheless feasible by targeted ultrasound.

Although each type of ACC is likely to reflect a different malformation spectrum, they appear to share the same prognosis of neurological development when they are isolated. Because instead when they are associated the prognosis depends largely on these anomalies. However, even in isolated cases of ACC have been reported a wide range of results ranging from almost complete normal to a severe impairment of neurological development manifesting through epilepsy or behavioral disorders. This heterogeneity can be explained at least in part by the great difficulty of confirming during the prenatal period, if the agenesis is isolated[66-78].

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