Corpus Callosum: embryological development, anomalies and their imaging presentation

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Learning objectives

• To present in a schematic way the embryological formation of the corpus callosum (CC) and the malformations that result from its interruption.

• To depict the characteristic magnetic resonance imaging (MRI) findings in different types of developmental anomalies of the CC and the concomitant changes in the brain morphology.
Background

The corpus callosum (CC) is the most important brain commissure connecting the cerebral hemispheres and facilitating the transfer of sensor, motor and cognitive information between them. The callosal maldevelopment is related to impaired brain function and in the great percent of the cases is associated with other brain anomalies. Thus, the morphology of the CC is an essential feature that indicates whether or not the brain development is normal [1, 2].

The order and timing of development of the corpus callosum are arguable and new theories exist about this question. It is widely accepted that the corpus callosum, the largest brain commissure, develops between 10\textsuperscript{th} - 20\textsuperscript{th} gestational weeks following specific embryological steps. Various causes can interrupt this process in different stages (during neuronal/glial proliferation, axonal growth, neuronal guidance and migration), leading to callosal malformations, associated with particular alterations in the brain structure [3].

As magnetic resonance imaging (MRI) is the modality of choice for best presentation of callosal maldevelopment, MR images, obtained from patients with congenital anomalies of the brain during a five years period, were retrospectively reviewed and cases with isolated and associated CC malformations were selected [1]. The callosal anatomy, embryology and main radiological features of the different types of its anomalies are summarised and presented.
Findings and procedure details

BRAIN COMMISSURES

The brain commissures, part of the three major types of connections of the neocortex (association, projection, and commissural fibers), are those white matter tracts that cross the midline and connect the two cerebral hemispheres. The largest commissure is the corpus callosum, and thus it has the greatest contribution to the structural formation and shape of the brain. It is divided into four well-known segments, from anterior to posterior: rostrum, genu, body and splenium. A fifth part is sometimes well seen and described - isthmus, connecting the body and the splenium (Fig. 1). The other two smaller interhemispheric fiber tracts are: 1. anterior commissure (AC) - connecting the temporal lobes, the olfactory areas and the amygdala and placed in front of the columns of the fornix and the anterior wall of the 3rd ventricle, above the optic chiasm; 2. hippocampal commissure (HC) - connecting the hippocampal formation and fornices and blended with the ventral surface of the callosal splenium [4]. Those three brain commissures develop almost simultaneously, navigated by complex cellular and molecular relations, and consequently, anomalies associated with the interruption of this process are rarely isolated. When the mechanisms regulating the commissural fibers formation and guidance fail, pathological formation of one or more commissures occurs. Callosal anomalies in most of the cases are accompanied by hippocampal commissure agenesis and in 50% by anterior commissure agenesis or hypoplasia [1, 2].

CALLOSAL ANATOMY

The corpus callosum has four segments, but can be subdivided into two major parts: the anterior one, consisting of the rostrum, genu, and body and the posterior one of splenium, with a place of fusion between them - isthmus (Fig. 1). Each callosal segment connects specific areas from the brain hemispheres, plays a specific role in the transfer of information and therefore facilitates the coordination between them [1].

The rostrum is the most anterior-inferior callosal part, forms the floor of the anterior horn of lateral ventricles and connects the fronto-basal orbital surfaces of the lobes.

The genu is the second part that is curved, lies behind the frontal lobe, and is formed of fibers that connect the prefrontal cortex and anterior cingulate area.

The trunk (body) is the main part of CC which connects the precentral motor cortex, insula and cingulate gyri and forms the roof of the central part of lateral ventricles.
*The isthmus* is the thinner area between body and splenium and connects pre- and postcentral sensory-motor gyri, as well as primary auditory areas.

*The splenium* is the most posterior massive part and connects the posterior parietal, infero-medial temporal (including posterior cingulate) and medial occipital lobes [1, 5] (Fig. 2).

**EMBRYOLOGY**

In the embryo (period from 2nd to 9th gestational weeks - g.w.) after the closure of the neuropore at 24-28th gestational days, the neural tube starts to form and to differentiate into the three primary encephalic vesicles: prosencephalon (forebrain), mesencephalon (midbrain) and rhombencephalon (hindbrain). The prosencephalon is later divided into two parts: telecephalon and diencephalon (Fig. 3). It is presumed that all telencephalic commissures cross the midline in a specific time through a distinct anatomical region - the commissural plate, which serves as a zone for axonal passage and provides a glial pathway to guide commissural axons [3, 6]. The telencephalon consists of two symmetric lateral evaginations - the cerebral hemispheres, which at 6-8 g.w. become separated by lamina terminalis at the rostral midline (Fig. 4). The dorso-superior part of lamina terminalis becomes thicker and transforms into lamina reuniens, which ventral part later develops into area septalis. As the hemispheric vesicles expand bilaterally, the dorsal part of lamina reuniens begins to fold into the median line, its sides come closer and form the massa commissuralis [6, 7]. The interhemispheric commissures develop sequentially from two sites: at 10 g.w. the *anterior commissure* from area septalis of lamina reuniens; and the *hippocampal commissure* and the *corpus callosum* later and dorsally from massa commissuralis (by interhemispheric fusion) (Fig. 5). The earliest callosal fibers, forming the genu and guided by pioneering cingulate axons, are considered to appear and penetrate the massa commissuralis at 11 to 12 g.w. [2, 6]. The callosal plate is well-defined in the fetus at 12-13 gestational weeks. It is widely assumed that the embryological growth of the corpus callosum follows roughly anterior to posterior path, beginning with the genu, followed by the body, splenium and completing with the rostrum at 20 g.w. [6]. A more detailed developmental sequence that was proposed is: posterior part of genu, anterior callosal body, anterior portion of genu at the same time as the posterior callosal body, splenium and rostrum [8, 9]. However, several studies exist which do not support these developmental theories, offering bidirectional growth after the initial formation of a part of the body [3, 7]. After the characteristic callosal shape with its four parts is achieved at 20 g.w., active axonal growth in the CC continues up to 30 g.w., initially by addition of fibers and later by myelination [1, 2].

The formation of the corpus callosum can be divided into three main stages:

1) commissuration, when fibers expand between the two telencephalic vesicles;
2) growth, when each callosal part is created;

3) maturation, pre- and postnatal axonal addition, elimination and myelination.

In newborns the myelination of the CC and its final volume are not yet completed. The thickness of the corpus callosum increases significantly throughout childhood and adolescence and reaches the target thickness at the age of 6 - 9 years. Growth in the anterior sections is most noticeable in the first years of life, while posterior splenial growth predominates later [1, 3].

**CALLOSAL ANOMALIES**

The corpus callosum passes through unique and complex developmental steps which can be divided into: neurogenesis, midline patterning, neuronal migration and specification, axon guidance, and post-guidance development. Various environmental and genetic causes can interrupt the developmental process of the CC in different stages, leading to congenital malformations associated with particular alterations in the brain structure and spectrum of neuropsychological deficits [2]. There are several major types of callosal anomalies: agenesis - complete absence of the corpus callosum; dysgenesis - partial formation, with missing segments; hypoplasia - preserved integrity and shape, but smaller size [1, 3, 6]. The specific congenital anomalies of the brain, and particularly of the corpus callosum, occur in a particular time of the embryological developent (Fig. 6).

1/ **Agenesis:** Agenesis of the corpus callosum (ACC) is most commonly associated with axons that fail to cross the midline and form atypical longitudinal fibers - Probst bundles and cause anomalous ventricle appearance (Fig. 7). However, in small number of cases axons do not form at all, thus no Probst bundles are present. ACC is a heterogeneous condition that can result from disruption of numerous developmental steps - from early midline telencephalic formation to post-guidance alterations [3].

2/ **Dysgenesis:** Typical dysgenesis of the corpus callosum (DCC) consists in the presence of the earlier-formed segments (genu, body) and absence of the later-formed ones (splenium, rostrum) (Fig. 8). In some patients with holoprosencephaly (semilobar or middle interhemispheric variant), condition that results from disruption of the prosopncephalic cleavage between 7-8 g.w., an atypical DCC can be observed. In such cases with interhemispheric fusion, due to lack of induction of the normal commissural plate, the normal sequence of callosal formation is not followed and therefore presence of the latest-formed segments and absence of the genu and part of body is noticed [6, 8] (Fig. 9).

3/ **Hypoplasia:** In cases with hypoplasia, the corpus callosum is thinner than general, but has a normal anterior-posterior extent [3] (Fig. 10).
The exact anatomy of the corpus callosum, all types of its malformations, as well as additional brain anomalies, can be evaluated accurately with MRI of the brain. The typical adult signal intensity of the corpus callosum is observed when its complete myelination (from posterior to anterior - genu last) is achieved after 1\textsuperscript{st} postnatal year - hyperintense on T1-weighted images and hypointense on T2-weighted images [1, 4]. MR diffusion tensor imaging (DTI), a noninvasive method based on the analysis of water diffusion in brain, accurately depicts the normal callosal interhemispheric connections, but also the abnormal alignment of the white matter tracts. It reveals the normal callosal white matter fibers that interconnect homotopic areas of both hemispheres. In cases with callosal maldevelopment, this technique represents precisely the disturbed and re-routed connections, such as the bilateral aberrant antero-dorsal running Probst bundles [2, 3] (Fig. 11, 12). In studies of individuals with partial callosal agenesis, DTI revealed extremely variable callosal connectivity, with many heterotopic tracts not seen in healthy subjects, for example 'sigmoid bundles' connecting the anterior frontal lobe with the contralateral parieto-occipital [3, 10].

Corpus callosum contributes mainly to the shape and size of the brain ventricles and as a result of its malformation specific changes in their structure, size and position in MRI are found. In callosal agenesis, the heterotopically positioned Probst bundles, oriented longitudinally and parallelly to the interhemispheric fissure and seen as hyper-at T1 weighted imaging and hypointense signal at T2WI, cause parallel orientation of the lateral ventricles and dilatation of the atria and occipital horns (colpocephaly) - 'tear drop' appearance on axial scans [2]. In axial MRI plane, these characteristic ventricular changes are described as "racing car sign", due to the resemblance of a race car (Fig. 13). Moreover, the commonly associated hypoplastic hippocampal formation leads to dilatation of the temporal ventricular horns. Another related brain alteration is the position of the third ventricle, as it may be abnormally dilated and bulging upward, giving the appearance of a cyst, or it may communicate with the interhemispheric cistern. This in coronary plane, along with the malrotated or absent cingulate gyrus that leads to narrowed elongated frontal horns, gives the sign of "moose head" or also called "Viking helmet" (Fig. 14). In some cases, in sagittal plane, abnormally formed gyri and sulci are found, converging radially and medially toward the 3\textsuperscript{rd} ventricle - "sunray appearance" [1, 6] (Fig. 7).

Callosal anomalies can be associated with many other brain malformations, from which we have encountered:

lipoma, schizencephaly, nodular heterotopia, polymicrogyria, porencephalic cyst, encephalocele, holoprosencephaly, Dandy-Walker malformation, hemimegalencephaly, hydrocephalus due to vein of Galen aneurysm, septo-optic dysplasia, septum pellucidum cyst, Chiari II malformation, rhombencephalosynapsis, lissencephaly and septum pellucidum agenesis (Fig. 15-36).
**Fig. 1:** Brain MRI of normal anatomy of the corpus callosum and its segments.

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Fig. 2: Callosal connections of the brain hemispheres.

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Fig. 3: Embryology of the brain and the corpus callosum.

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**Fig. 4:** Embryology of the brain - lamina terminalis appearance at 6-8 g.w.

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**Fig. 5:** Embryology of the interhemispheric brain commissures - start at 10 g.w.

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Fig. 6: Developmental anomalies of the brain cleavage and commissures, dependent on the specific embryological period.

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**Fig. 7:** A. Sagittal T2WI: Agenesis of all commissures (AC, CC, HC). Radially oriented gyri - 'sunray appearance'. B. Coronal T2FLAIR: ACC causing 'moose head sign' of the ventricles. C. Axial T2WI: Colpocephaly - 'racing car sign' of the ventricles.

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Fig. 8: A. Sagittal T1WI: Dysgenesis of the CC (absent posterior truncus, splenium and rostrum). Radially oriented gyri. B. Coronal T2FLAIR: DCC causing 'moose head sign' of the ventricles. C. Axial T2WI: Colpocephaly - 'racing car sign' of the ventricles.

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Fig. 9: A. Sagittal T2WI Atypical dysgenesis of the CC (anterior segments: rostrum, genu absent; posterior: truncus and splenium present). Azygos anterior cerebral artery - absent anterior communicating artery, single trunk of A1 segments (yellow arrow). B. Coronal FLAIR Holoprosencephaly - fusion of part of the frontal lobes. C. Axial T2WI Holoprosencephaly - hypoplastic frontal horns; dilated and fused occipital horns.

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**Fig. 10:** A. Sagittal T2WI Hypoplasia of the corpus callosum. B. Coronal T2FLAIR Septum pellucidum cyst. C. Axial T2WI Septum pellucidum cyst. Dilated occipital horns - colpocephaly.

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**Fig. 11:** MRI Diffusion tensor imaging: on the left - red-colored normal fibers of the corpus callosum connecting the two hemispheres, and on the right - missing CC in dysgenesis with abnormally formed green-colored parallel Probst bundles.

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**Fig. 12:** MRI Diffusion tensor imaging: on the left - normal red-colored fibers of the corpus callosum (genu and splenium); and on the right - partially developed corpus callosum (red-colored genu).

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**RACING CAR SIGN = COLPOCEPHALY**

**Fig. 13:** Racing car sign in patient with dysgenesis of the corpus callosum.

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Fig. 14: Moose head sign in patient with dysgenesis of the corpus callosum.

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Fig. 15: A. Sagittal/T1WI: Agenesis of the corpus callosum. Lipoma (tubulonodular type) in the interhemispheric fissure. B. Coronal/T2FLAIR: ACC - 'moose head sign'. Lipoma - hyperintense. C. Axial/fat supression: ACC - 'racing car sign' of the ventricles. Lipoma - supressed signal.

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Fig. 16: A. Sagittal/T2WI: Agenesis of the corpus callosum - radially oriented gyri. B. Coronal/3DT1: Schizencephaly (open-type) - parietally on the left. ACC - 'moose head sign'. C. Axial/3DT1: Heterotopy. ACC - racing car sign.

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Fig. 17: A. Sagittal/T2WI: Agenesis of all commissures. Radially oriented gyri. Polymicrogyria. B. Coronal/T2FLAIR: ACC - 'moose head sign' of the ventricles. C. Axial/T2WI ACC - 'racing car sign' of the lateral ventricles. Polymicrogyria. Nodular heterotopia.

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Fig. 18: A. Sagittal/T1WI: Agenesis of the corpus callosum. B. Coronal/T2FLAIR: Porencephalic cyst frontally. C. Axial/T2WI: Porencephalic cyst. ACC - colpocephaly. Hydrocephaly. Absent septum pellucidum.

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Fig. 19: A. Sagittal/T2WI: Agenesis of the CC. Frontal encephalocele. B. Sagittal/T2WI & C. Axial/3DT1WI: Cyst in the area of the right orbit. Enlarged lateral ventricle.

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Fig. 20: A. Sagittal/T2WI: Dysgenesis of the corpus callosum (present anterior part; absent posterior). B. Coronal/T2FLAIR: Holoprosencephaly - fused hemispheres. Hypoplastic frontal horns. Absent septum pellucidum. C. Axial/T2WI: Holoprosencephaly - connection of part of the frontal and parietal lobes - middle interhemispheric variant.

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Fig. 21: A. Sagittal/T1WI Dysgenesis of the corpus callosum. B. Coronal/FLAIR & C. Axial/T2WI: Schizencephaly (open type) - cleft between the left lateral ventricle and the parietal cerebrospinal fluid. DCC - 'moose head sign'.

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Fig. 22: A. Axial/T2WI Schizencephaly (open-lip-type), dural defect and epidural liquor collection. Dysgenesis of the corpus callosum. Septum pellucidum agenesis. B. Sagittal & C. Coronal FLAIR: Schizencephaly frontally on the right.

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Fig. 23: A. Sagittal/T2WI; B. Coronal/T2FLAIR; C. Axial/T2WI: Hypoplasia of the CC. Dandy-Walker variant - hypoplasia of vermis. Cystic dilatation of 4th ventricle and retrocerebellar fossa.

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**Fig. 24:** A. Sagittal/T2WI; B. Coronal/T2WI & C. Axial/T2WI: Hypoplasia of the corpus callosum. Dandy-Walker malformation - cerebellar hypoplasia. Enlarged retrocerebellar cyst.

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Fig. 25: A. Sagittal/T2WI: Hypoplasia of the corpus callosum. Hypoplasia and cephaled rotation of the vermis. B. Coronal/T1WI & C. Axial/T2WI: Enlarged 4th ventricle, extending posteriorly and communicating with the dilated retrocerebellar fossa.

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Fig. 26: A. Sagittal/T1WI: Dysgenesis of the CC (absent part of body, splenium and rostrum), hypoplastic developed parts. Dandy-Walker variant: hypotrophic vermis, enlarged retrocerebellar cystern. B. Coronal/T2FLAIR & C. Axial T2WI: Lissencephaly - smooth brain surface. Septum pellucidum cyst.

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Fig. 27: A. Sagittal/T1WI: Hypoplasia of the corpus callosum. B. Coronal/T2FLAIR & C. Axial/T2WI: Hemimegalencephaly - overgrowth of the right cerebral hemisphere.

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**Fig. 28:** A. Sagittal/T1WI: Hypoplasia of the corpus callosum. Vein of Galen aneurysm. B. Coronal/3DTOF venous & C. Axial T2W: Vein of Galen aneurysm causing hydrocephalus and hypoplasia of CC.

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**Fig. 29:** A. Sagittal/T2WI: Hypoplasia of the CC. B. Coronal/FLAIR & C. Axial/T2WI: Septo-optic dysplasia - hypoplastic optic nerves and globes.

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Fig. 30: A. Sagittal/T1WI: Hypoplasia of the CC. B. Axial/T2WI: Colpocephaly. Septum pellucidum cyst. C. Coronal/T2WI: Septum pellucidum cyst

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Fig. 31: A. Sagittal/T2WI: Hypoplasia of the corpus callosum. Arnold-Chiari II malformation - small posterior fossa and descent medulla, cerebellar vermis and fourth ventricle through foramen magnum. B. Coronal/T2FLAIR & C. Axial/T2WI: Chiari II. Hydrocephalus.

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Fig. 32: A. Sagittal/T2WI: Hypoplasia of the corpus callosum. Arnold-Chiari II malformation - displaced medulla and cerebellar tonsils through foramen magnum and lumbar spina bifida defect (not shown). B. Axial/T2FLAIR & C. Axial/T1FLAIR: Rhombencephalosynapsis - fusion between the two cerebellar hemispheres.

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Fig. 33: A. Sagittal/T1WI: Hypoplasia of the corpus callosum and dysgenesis (not well presented anterior parts of the CC and splenium). Chiari type II - herniation of the cerebellum through foramen magnum. B. Axial/T2WI: Hydrocephalus. C. Sagittal/T2WI: Lumbar spine malformation with myelomeningocele.

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Fig. 34: A. Sagittal/T1WI: Dysgenesis of the corpus callosum with hypoplasia of the truncus and splenium. Hypotrophic cerebellum. B. Coronal/T2FLAIR: Enlarged interhemispheric fissure. Periventricular gliosis due to hipoxic-ischemic encephalopathy. C. Axial/T2WI: Ventriculo-peritoneal shunt on the right due to hydrocephaly.

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**Fig. 35:** A. Sagittal/T2WI Hypoplasia + dysgenesis - not well-defined splenium and rostrum. B. Coronal/T2FLAIR & C. Axial/T2WI: Lissencephaly - absent cortical sulci causing smooth brain surface.

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Fig. 36: A. Sagittal/T2WI: Dysgenesis of CC - absent splenium and hypoplastic developed segments. B. Coronal T2FLAIR & C. Axial/T2WI: Septum pellucidum agenesis.

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Conclusion

The corpus callosum has a fundamental role in the structural formation and connection of the two hemispheres and therefore is an essential indicator for normal brain formation. The simple depiction of its developmental process facilitates the understanding of the radiological manifestation of the callosal anomalies and the associated brain alterations. We have revised and illustrated schematically the embryological development of the corpus callosum, its abnormalities causing typical brain changes and the associated brain malformations. MRI findings, as well as diffusion tensor images, were presented and correlated to the specific callosal maldevelopment.
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