Crossroads: history of the corpus callosum.

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Learning objectives

To describe the histopathological characteristics of the corpus callosum that may determine the type of pathology that can affect it.

To review the lesions that may affect the corpus callosum and classify them according to etiology and illustrate them.
Background

The corpus callosum is the most prominent forebrain commissure which spans much of the frontal and parietal lobes from the anterior commissure rostrally, to the posterior commissure posteriorly. It is formed by topographically distributed neuronal fibers with different calibers that interconnect homologous areas of the cerebral hemispheres.

The corpus callosum holds his name from its compactness, and that constitutes a barrier to the flow of interstitial edema and tumor spread. This way, only congenital or aggressive tumors may affect it (lipoma, glioblastoma multiforme, and lymphoma). This feature also conditions and increased susceptibility to acute axonal injury in head injuries.

Myelinated axon composition makes it a target for demyelinating diseases, both primary such as multiple sclerosis and secondary, like progressive multifocal encephalopathy (PML) acute disseminated encephalomyelitis (ADEM) or Marchiafava-Bignami disease (MBD).

On the other hand, the corpus callosum is less sensitive to ischemia since it is not gray matter, so that ischemic events are rare and usually form part of the vascular territory in large-vessel strokes. It has also been described hemorrhages in the corpus callosum.
Developmental abnormalities

Agenesis of corpus callosum

The corpus callosum (CC) begins to develop around 8-12 weeks of gestation from the lamina reuniens of His in the region of the genu and progresses in cranio-caudal direction to the splenium. The last part to develop is the rostrum, which finally closes off the residual sulcus medianus telencephali medii about 18-20 weeks of gestation.

Depending on the time of gestation in which there is an insult, the developmental abnormalities of the CC can range from complete agenesis (Fig. 1 on page 13) to different degrees of partial agenesis (Fig. 2 on page 13). Thus, partial agenesis involves the posterior elements of the CC, and the presence of rostrum makes this possibility improbable.

Holoprosencephaly (Fig. 3 on page 14) is an exception to this rule and often have the posterior parts of the CC preserved. Oba and Barkovich (1995) hypothesized that and the presence of an interhemispheric fissure is necessary for callosal formation, and the presence of a dorsal cyst in this pathology may interfere in it.

Agenesis of the CC (ACC) is commonly associated with colpocephaly and atypical fiber bundles (Probst’s Bundles) which runs parallel and laterally to the interhemispheric fissure.

Actual reports place ACC at 1:4000 live births and 3-5% of patients who had undergone an imaging technique due to neurodevelopmental disorders. ACC is commonly associated with syndromes and malformations such as lipoma, Dandy-Walker spectrum, heterotopias, schizencephaly (Fig. 4 on page 14), lissencephaly, Chiari II malformation, Aicardi syndrome (triad of infantile spasms, ACC and pathognomonic chorioretinal lacunae), etc.

On imaging (Fig. 1 on page 13), parallel lateral ventricles with occipital horns often dilated (colpocephaly) are demonstrated. On coronal slices, anterior horns are arranged in a trident shape resembling a "viking helmet" or "moose head" and compact longitudinally oriented white matter tracts which are brighter than other myelin on T1WI, constitutes the Probst’s bundles. Paramedian gyri are arrayed radially pointing to third ventricle in sagital views.
Differential diagnosis must be established with pathologies which may lead to destruction of the corpus callosum (trauma, callosotomy), hypoxic ischemic encephalopathy, infarction and metabolic diseases such as Marchiafa-Bignami disease with necrosis.

**Lipoma**

Pericallosal lipomas account for up to 65% of intracranial lipomas that are considered developmental lesions of the central nervous system found in only 1 in 2,500 to 1 in 25,000 autopsies. They can represent incidental findings but association with seizures are frequently around 50% with and are frequently associated with callosal anomalies.

The diagnosis is made on CT or MRI depicting a round to ovoid, homogeneous and well-defined lesion with fat characteristics (hypoattenuation on CT and high signal on T1WI and T2WI with signal decrease on fat suppression sequences on MRI) and no enhancement (Fig. 5 on page 15).

The differential diagnosis includes fatty components lesions, such as intracranial fatty falx cerebri, dermoid cysts, teratomas and lipidic contrast medium remnants from previous mielographies hyperintenses on T1WI.

**Tumors**

**Glioblastoma multiforme**

Glioblastoma multiforme (GBM) (WHO grade IV astrocytoma) is the most common primary brain malignancy, accounting for 12%-15% of all intracranial neoplasms and about 50% of astrocytomas. It is usually found in the supratentorial white matter of cerebral hemispheres of adults between 45 and 70 years of age, and commonly spreads via direct extension through white matter tracts, including the corpus callosum (giving the classic butterfly appearance) to involve the contralateral hemisphere.

Clinically, patients may present focal neurological deficits, increased intracranial pressure symptoms or seizures.

Conventional gadolinium-enhanced MRI is the standard technique for the evaluation of glioblastoma and typically demonstrates a large, heterogeneous mass with central necrosis, hemorrhage, with thick irregular enhancing margins and surrounding edema (Fig. 6 on page 16).
Differential diagnosis includes primary central nervous system (CNS) lymphoma and toxoplasmosis in AIDS, and metastases (rare, more frequent as a secondary regional spread from a adjacent metastatic focus).

**Lymphoma**

Primary central nervous system lymphomas (PCNSL) are rare aggressive neoplasms of the brain, accounting for only 1% of malignant CNS tumors. Approximately 2 - 6% of patients with HIV will develop PCNSL demonstrating a strong association with HIV/AIDS and immunocompromised states. They are almost always of the B-cell non-Hodgkin’s type and the most common locations include the corpus callosum, periventricular white matter and deep gray matter.

CT scans usually show commonly multiple lesions with high attenuation and virtually all lesions show homogeneous contrast enhancement (Fig. 7 on page 18). On MRI lesions are clearly delineated masses that appear isointense to hypointense on T1WI and relatively hypointense on T2WI with less peritumoral edema than GBM. Rarely, necrosis, cyst formation, calcification, and hemorrhage can be seen, and "vanishing" after steroid administration is characteristic.

Toxoplasmosis in AIDS, GBM and acute disseminated encephalomyelitis (ADEM) are among the differential diagnosis.

**Trauma**

**Diffuse axonal injury**

Diffuse axonal injury (DAI) is a consequence of most forms of traumatic brain injury, especially results from the brain moving back and forth in the skull as a result of rotational acceleration or deceleration. Histologically, DAI is characterized by widespread damage to axons in several brain regions, including gray-white matter interface of the cerebral hemispheres, the dorsolateral aspect of the rostral brainstem, and the corpus callosum (usually in posterior body and splenium).

DAI is clinically presented as loss of consciousness at the time of the accident. On CT scans hemorrhagic foci can be observed, but MRI is much sensitive in identifying tissular injuries as high signal intensities in T2WI and FLAIR sequences. After 4 days, hemorrhagic lesions are better depicted in T1WI as hyperintense foci, and T2* is the best sequence to look for chronic haemoglobin degradation products. Lesions can also be classified as vasogenic edema, cytotoxic edema or central hemorrhage by DWI. MR
Spectroscopy can depict injury in brain that appears normal on imaging and is useful for predicting long-term outcomes.

Differential diagnosis with strokes should be based on trauma history and distribution of lesions in corpus callosum.

**Inflammatory demyelinating diseases**

**Multiple sclerosis**

Multiple sclerosis (MS) is an acquired chronic relapsing demyelinating disease involving the central nervous system and it is by definition disseminated in space and also in time. MS usually affects young women with different longitudinal patterns of disease. Affected patients may suffer sensory or motor symptoms, including cranial nerves.

The plaques (Fig. 8 on page 19) are typically small and ovoid, and characteristically involve the periventricular white matter arranged perpendicularly to lateral ventricles (Dawson’s fingers), internal capsule, corpus callosum and callososeptal interface (highly sensitive and specific for MS), and pons, although lesions can be found anywhere in the white matter and less commonly even in gray matter. The involvement of corpus callosum on MRI has been reported up to 93%, and atrophy can coexist in long-term MS. CT is unspecific but in the appropriate clinical scenario, typical hypodense areas in a typical distribution may suggest the diagnosis. MRI constitutes the optimal radiologic technique for diagnosis and follow-up of MS. The lesions described are isointense to hypointense in T1WI, hyperintense in T2WI and FLAIR and acute lesions can show enhancement and restricted diffusion.

Differential diagnosis for callosal lesions is made with other demyelinating diseases such as MBD.

**Progressive multifocal leukoencephalopathy**

PML is a progressive demyelinating disorder which results from JC virus infecting oligodendrocytes in immunosuppressed status, especially in AIDS (prevalence of 5% in autopsies). PML leads to a progressive neurologic decline that consists of cognitive impairment, altered mental status and personality changes that used to result in death in 90% of cases within 1 year without treatment.

Lesions are typically confluent, bilateral asymmetric, involving supratentorial white matter with frequently affectionation of subcortical U-fibers and middle cerebellar peduncle, but may
be unilateral or single lesions. Less common sites of involvement are corpus callosum, brainstem, internal and external capsule or even grey matter in thalamus and basal ganglia.

On CT lesions can be seen as hypodense areas in the mentioned regions, which are shown as hypointense on T1WI and hyperintense in T2WI and FLAIR. Commonly there is no enhancement, but faint peripheral enhancement may be seen or even increase after antiretroviral treatment administration (Immune reconstitution inflammatory syndrome). On DWI in acute lesions a peripheral incomplete rim of restriction may be seen, and signifies active infection.

Differential diagnosis is made with stroke for single lesions, HIV encephalopathy (more symmetrical distribution) or even lymphoma or GBM when enhancement is observed.

**Acute disseminated encephalomyelitis**

ADEM is a severe monophasic inflammatory demyelinating disease of the white matter, usually after a close viral infection or vaccination. It is clinically presented by an abrupt onset of multifocal non-specific neurological deficits and often affects children, however ADEM can occur at any age.

The demyelinating lesions are ill-defined, bilateral, confluent and asymmetrical and are usually located in the subcortical and central white matter, but involvement of callososeptal interface is unusual. As other demyelinating lesions, they appear as hypodense areas on CT, hypointense in T1WI and hyperintense in T2WI and FLAIR. Reports of gadolinium enhancement are inconsistent, so it must be variable.

The most important differential diagnosis must be made with MS and there have been many attempts to differentiate both diseases by imaging techniques. Thus, Brass et al. (2003) reported that the involvement of the corpus callosum and periventricular white matter in children is more frequent in MS than in ADEM. On the other hand, it has been used techniques such as proton spectroscopy, where Sira et al. (2010) found specific patterns in ADEM (reduced myo-inositol in the acute phase and its changes over time). Callen et al. (2009) also proposed MS diagnostic criteria in pediatric patients with MRI (any two of absence of a diffuse bilateral lesion pattern, presence of black holes, and presence of two or more periventricular lesions). The differential diagnosis may also include Susac’s syndrome, a rare microangiopathy which affects the brain, retina and cochlea.

**Metabolic demyelinating diseases**
Marchiafava-Bignami disease

MBD is a rare toxic-metabolic disease described in chronic alcoholics which leads to primary demyelination of the corpus callosum. Acute MBD can present mental confusion, disorientation, neurocognitive deficits and seizures while chronic MBD is characterized by dementia. Although the pathogenesis is unclear, toxic agents in low quality red wine associated to vitamin B complex deficiencies has been postulated as potential causes.

Histologically MBD includes layered necrosis, degeneration in different degrees with preservation of axonal to the necrosis and cystic cavitations. It has also been described cortical involvement as cortical laminar necrosis and gliosis, mainly in the third layer, associated with the callosal lesion, and probably secondary to it.

The demyelination in MBD is seen as hypoattenuation areas in CT, hipointensity in T1WI and hyperintensity in T2WI and FLAIR sequences and involves characteristically the body of the corpus callosum, followed by the genu and finally the splenium. Acute demyelination can associate restricted diffusion in DWI due to cytotoxic edema in the acute stage. In the chronic phase, the corpus callosum appears atrophic and the lesions can become cystic and well marginated (Fig. 9 on page 16). Occasionally they may be reversible.

The radiologic differential diagnosis includes multiple sclerosis, diffuse axonal injury and callosal infarction.

X-linked adrenoleukodystrophy

X-linked adrenoleukodystrophy (ALD) is a rare metabolic disorder secondary to peroxisomal enzyme dysfunction which leads to very long chain fatty acids (VLCFA) deposition and CNS, adrenal glands and testicles failure. There has been reported high variation in incidence, from 1/20.000 to 1/200.000, and classically affects young males.

According to age at symptoms onset and mainly involved organs, ALD has been classified in childhood cerebral X-linked ALD (37%), adolescent cerebral X-linked ALD, adrenomyeloneuropathy (32%), adult cerebral X-linked ALD, Addison disease-only type and asymptomatic type.

Diagnosis is made by VLCFA analysis in serum, but MRI is an important tool to detect early CNS lesions and differentiate cerebral X-linked ALD from other forms. Different patterns of involvement have been described, but the classical (and the most common) affects peritrigonal white matter in the parieto-occipital lobes and splenium of the corpus callosum. On MRI, these lesional areas are depicted as hypointense on
T1WI and hyperintense in T2WI and FLAIR, with a characteristic peripheral enhancement representing active inflammatory demyelination (Fig. 10 on page 17).

Differential diagnosis can be made with periventricular leukodystrophy, neonatal hypoglycaemia, white matter disease with lactate, metachromatic leukodystrophy and Alexander disease.

**Vascular disease**

**Infarction**

As mentioned before, the corpus callosum is a compacted white matter tract, so is less sensitive to ischemic injury than grey matter and therefore infarction is rare.

The corpus callosum is supplied mainly by anterior and posterior pericallosal arteries, branches of anterior and posterior cerebral arteries respectively. It has also been demonstrated subcallosal or median callosal arteries rising from anterior communicating artery. The central areas are supplied by short penetrating arterioles unlike centrum semiovale and basal ganglia, which are irrigated by long endarteries. Thus, lacunar infarction of corpus callosum is rare, and when it is affected by ischemia, it is in the context of large-vessel strokes being part of the tributary territory. It has been reported corpus callosum involvement in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and in giant cell arteritis. Epelman et al. (2011) also reported corpus callosum involvement in neonates with hypoxic-ischemic injury.

On imaging doesn't differ from other regions ischemic lesions, presenting as hypodense lesions in CT, hypointense in T1WI, hyperintense in T2WI and FLAIR and associates diffusion restriction in acute phase.

Differential diagnosis should be made with lacunar infarcts from other entities such as trauma or demyelinating processes based in the grade of involvement, thus in ischemic lesions the whole thickness of the corpus callosum is affected, while in demyelinating diseases the injury extends in caudo-craneal direction.

**Hemorrhage**

Hemorrhage in the corpus callosum may be secondary to an anterior communicating artery or distal anterior cerebral artery aneurysm rupture or to a corpus callosum arteriovenous malformation bleeding. They are usually associated with subarachnoid or
intraventricular hemorrhage, and imaging findings are the same as bleeding in other locations.

**Iatrogenic**

We have reviewed many diseases from different etiologies affecting the CC, but it can be involved in addition by other type of pathologies or treatment. Thus, we could find CC lesions in diseases that we wouldn't expect and we should be aware of them to avoid its misinterpretation. In this context we can mainly distinguish injury of the CC secondary to radiotherapy, chemotherapy and to ventricular drainage.

Therapy-induced cerebral necrosis (TCN) is secondary to radiotherapy with or without chemotherapy, which are commonly associated as neoadjuvant and palliative treatment in CNS or extra-CNS tumors. Risk factors to develop TCN are the method of radiation delivery, total dose, fraction size, treatment volume, patient age and concomitant chemotherapy.

Rogersat al. 2011 retrospectively reviewed 44 patients who underwent this kind of treatment and assessed the different patterns of histologically proven TCN. In this way, they found that both cortical as white matter TCN lesions demonstrated contrast enhancement, mainly in the latter in periventricular/subependymal region and corpus callosum. They also reported that most frequent peripheral enhancement morphology was in "spreading wavefront", and in interior enhancement was "Swiss cheese/soap bubble", accounting the 93% of the lesions with mass effect. As all the lesions showed enhancement, it is important to differentiate TCN from recurrence, since they have different therapeutic management.

Patients with ventricular drainage can also suffer CC lesions after catheter placement apart from those produced by direct damage. Lane et al. 2001 reviewed previous reports and also contributed with a 9 patient's series and found that there were signal changes (hyperintensity in T2WI and hypointensity on T1WI) in the anterior and posterior part of the body in long-standing obstructive hydrocephalus after shunting. The hypothesis presented is that these changes are secondary to long-term compression of the fibers of the CC against the lower surface of the falx. These lesions have no apparent clinical repercussion.

**Miscellanea**

**Reversible focal splenium lesions**
Reversible focal splenium lesions, recently called reversible splenium lesion syndrome (RESLES) by Garcia-Monco et al. (2008), have been actually described in seizures, antiepileptic drugs withdrawal, metabolic disorders (hypoglycemia or hypernatremia), influenza encephalitis/encephalopathy, high-altitude cerebral edema (HACE), staphylococcal meningitis, legionnaire's disease, hemorrhagic fever, malnutrition, radiotherapy and neoplasm such as acute lymphocytic leukemia, spinal meningeal melanocytoma, and esophageal cancer.

Garcia-Monco et al. postulates that RESLES is a distinct clinicoradiological syndrome of varied etiology and benign course except in those patients with an underlying severe disorder, whose mechanisms still remains unclear.

RESLES show the same characteristics on MRI in the different pathologies: hyperintense on T2WI and FLAIR, slightly hypointense on T1WI and hyperintensity on DWI with low ADC.
**Fig. 1:** Corpus callosum agenesis. (a) Axial T2WI shows absence of corpus callosum (arrow) with dilated occipital horns (colpocephaly) and compact longitudinally oriented white matter tracts in "b" (Probst's bundles, arrows). (c) Coronal FLAIR depicts the anterior horns in a trident shape (moose head). (d) Mid sagittal T2WI of another patient shows lack of corpus callosum, and parasagittal (e) demonstrate paramedian gyri arrayed radially pointing to third ventricle (arrows).

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**Fig. 2:** Corpus callosum partial agenesis. Mid sagittal T1WI in different patients shows different degrees of agenesis. Note that it is always involved posterior elements of the corpus callosum in typical partial agenesis.

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**Fig. 3:** Holoprosencephaly. Sagittal T1WI show alobar holoprosencephaly with rudimentary frontal lobes fused and absence of corpus callosum.

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Fig. 4: Schizencephaly. Sagittal T1WI depict a cleft of frontoparietal area, connecting subarachnoid space with third ventricle and absence of great part of the body of the corpus callosum. Note also a round hypointense mass in cerebellum, which demonstrated to be a pulmonary neoplasm metastasis.

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**Fig. 5:** Callosal and pericallosal lipoma with underdeveloped splenium. (a) Mid sagittal and (b) axial T1WI show a callosal lipoma located in the splenium. (c) Mid sagittal T1WI depict a pericallosal lipoma covering the superior surface of the corpus callosum. The splenium has not been completely developed.

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**Fig. 6:** Glioblastoma Multiforme. (a) Sagittal T1WI and (b) coronal T1WI after administration of gadolinium show an heterogeneous mass with central necrosis, thick irregular enhancing margins in the body of the corpus callosum. (c) Coronal FLAIR depict the hyperintense mass with surrounding vasogenic edema.

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Fig. 9: Marchiafava-Bignami disease. In coronal FLAIR (a) and axial T2WI (b) the corpus callosum appears hyperintense and associates restricted diffusion in DWI (c). In the 3 month follow up study, the coronal FLAIR (d) and axial T2WI (e) demonstrate the thinner corpus callosum, which is now iso- to slightly hyperintense relative to the normal white matter and shows cystic changes (arrows). In axial DWI (f) we can appreciate that there is not associated restricted diffusion.

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**Fig. 10:** X-linked adrenoleukodystrophy. Demyelination of the peritrigonal white matter (black arrows) in the parieto-occipital lobes and splenium of the corpus callosum (yellow arrows) in (a) axial T2WI and (b) coronal FLAIR depicted as hyperintense areas. (c) Axial enhanced-T1WI show hypointense lesional areas with the characteristic peripheral enhancement representing active inflammatory demyelination (red arrows).

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**Fig. 7:** Lymphoma. Axial nonenhanced CT (a, b) and after contrast administration (c,d) show a high attenuation mass with homogeneous enhancement in perialtrial white matter (white arrows) and central necrosis(red arrows) spreading contralaterally through the splenium.

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Fig. 8: Multiple sclerosis. Parasagittal FLAIR image show multiple small and ovoid hyperintense lesions involving the periventricular white matter arranged perpendicularly to lateral ventricles (Dawson´s fingers), corpus callosum and the cerebellar peduncle.

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Conclusion

The corpus callosum has a slightly different pathologic substrate from the rest of the white matter, and different from the gray matter. This determines a particular involvement by the different pathologies and their knowledge allows us a better understanding to help us to narrow the differential diagnosis and obtain a greater diagnostic accuracy.
References


