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Review

Corpus callosum and epilepsies

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ABSTRACT

Purpose: Corpus callosum (CC) is the largest forebrain commissure. This review focuses on the significance of CC for seizure disorders, the role of CC in seizure spread and the surgical disruption of callosal fibers (callosotomy) for treatment of patients with drug-resistant epilepsy.
Methods: Personal experience/extensive literature review.
Results: Structural CC pathologies comprise developmental abnormalities, callosal involvement in identified disorders, transient imaging findings and microstructural changes. Epilepsies are reported in up to two thirds of patients with complete or partial CC agenesis (AgCC). However, AgCC per se is not indicative for seizure disorders. Moreover, additional malformations of cortical development (MCD) are causal. Microstructural CC abnormalities are detected by advanced imaging techniques, are part of diffuse white matter disturbances and are related to cognitive deficits. The etiological significance remains unexplained. However, they are also found in non-epileptic benign and transient disorders. In drug-resistant epilepsies with violent drops to the floor ("drop seizures") callosotomy may be beneficial in seizure reduction. Since the EEG after callosotomy exhibits a single seizure focus in up to 50% of patients, consecutive resective surgical methods might be successful.
Conclusion: CC is part of cerebral white matter and anomalies cannot act per se as seizure onset zone. Imaging techniques demonstrate additional lesions in patients with epilepsies. CC is the major pathway for seizure generalization. Therefore, callosotomy is used to prevent generalized drop seizures.

1. Introduction

Corpus callosum (CC) is by far the largest forebrain commissure with about 190 million axons crossing the midline [1]. The final shape is completed by 20 weeks post-conception, although structural changes continue until adolescence [2]. Physiological functions are mediated by excitatory and/or inhibitory influences on interhemispheric transfer and include bilateral movements, integration of bilateral sensory and visual information, specialization of language and handedness, emotion, behavior, cognition, memory and complex integrative functions [3].

Acute diffuse and multifocal CC alterations due to acquired disorders may result in severe neurological deficits [4], whereas chronic isolated CC anomalies typically exhibit no major neurological symptoms [5]. Abnormal callosal imaging findings can be seen in persons with epilepsies (PWE). This review focuses on the significance of CC for seizure disorders, the role of CC in seizure spread and the surgical disruption of callosal fibers (callosotomy) for treatment of patients with drug-resistant epilepsy.

2. Structural abnormalities

Structural CC pathologies can be subdivided into developmental abnormalities, callosal involvement in acquired brain disorders, transient changes and microstructural findings.

Developmental CC anomalies typically represent agenesis of CC (AgCC).

Neonatal and prenatal imaging studies suggest that AgCC occurs in at least 1:4000 live births [6]. Agenesis of CC (AgCC) can be complete or partial [1,6]. Complete AgCC is divided into type 1 and 2 according to the presence (type 1) or absence (type 2) of uncrossing axons forming the so-called Probst bundle [7]. AgCC can occur isolated or may be associated with other disorders of brain development. These typically involve the midline and telencephalic structures and consist of malformations of cortical development (MCD) including polymicrogyria, lissencephaly, pachygyria, schizencephaly, focal cortical dysplasia (FCD), midbrain–hindbrain malformations and others (Table 1) [2,7–9]. For

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Table 1
Telencephalic malformations additional to CC anomalies. For additional malformations of midline structures see references [1,7,9,122,131].

Malformation	References
Lissencephaly	[1,7,9,122,123,124,125,126]
Pachygyria	[7,9,122,127]
Gray matter heterotopia	[7,9,122,128,129]
Schizencephaly	[10,122]
Polymicrogyria	[1,7,9,13,130]
Focal cortical dysplasia	[1]
Cortical malformations (unspecified)	[9,131]

instance, Aicardi syndrome initially described in 1965 [10], is characterized by pathognomonic chorioretinal lacunae identified on ophthalmologic examination, skeletal findings and typical brain MRI findings comprising dysgenesis of the corpus callosum, gross cerebral asymmetry with polymicrogyria or pachygyria, periventricular and intracortical gray matter heterotopia, choroid plexus papillomas, ventriculomegaly, and intracerebral cysts. Aicardi syndrome appears to be an X-linked dominant disorder with lethality in males, but no gene or candidate region on the X chromosome has been definitively identified [11].

Overall, identifiable genetic causes are found in up to 45% of patients with AgCC, including chromosomal anomalies in about 10% and recognizable genetic syndromes in up to 35% of patients, respectively 2,6,12,14–18. Moreover, exogeneous causes like infectious, vascular and toxic factors may also contribute to AgCC [6]. Isolated AgCC exhibits subtle or no clinical symptoms and receives medical attention only accidentally. Hence, the incidence is very likely underestimated [9]. Up to two thirds of patients with developmental CC anomalies are symptomatic with epilepsies [19]. Seizures, varying degrees of cognitive deficits and dysmorphias are symptoms of accompanying telencephalic lesions [20]. Developmental syndromes in combination with telencephalic brain anomalies include all steps of cortical development, whether from genetic or acquired etiologies [2]. Patients with an identifiable seizure onset zone, especially those related to restricted FCD might be amenable to resective epilepsy surgery.

Callosal involvement in acquired disorders has to be separated from developmental AgCC due to exogenous factors. Renard et al. [4] reviewed vascular, hemorrhagic, demyelinating, infectious, metabolic and neoplastic lesions located in CC. Brain trauma may lead to diffuse CC changes [21–23]. CC lesions per se are difficult to diagnose clinically and are frequently detected only by brain imaging. In rare cases they may represent an accidental finding unrelated to the condition leading to structural tests.

Small ovoid **transient anomalies in the splenium of CC** were detected in PWE [24,25,26,27,28,29,30,31,32]. Several etiological factors were suspected, none was proven [33]. Splenial transient MRI changes are not specific for epilepsies or seizures since they also might occur with encephalitis/encephalopathy [34–39], with intake of antiepileptic drugs for psychiatric indications without seizures [40], and after brain radiation [41]. Renard et al. [4] postulated an entity at its own called Mild Encephalitis with a Reversible Splenial Lesion (MERS). Common to these transient CC lesions is the benign course without permanent consequences.

Microstructural CC changes were demonstrated by diffusion tensor imaging (DTI) and volumetric methods [52–54]. Reduced total callosal/scull area ratios, abnormal thickness of different CC areas, displacement and disrupted microstructures and microhemorrhagic lesions are illustrated. Beside epilepsies, status after very preterm birth [42], cognitive disorders [43], posttraumatic brain injuries [44], disorders with spasticity [45,46], autism [47,48], chronic carbon monoxide intoxication [49] and others exhibited statistical group differences in the microstructure of CC (for summary see [50,51]).

Microstructural CC changes in persons with epilepsies. Callosal abnormalities per se are not indicative for seizure disorders. Seizures generally hint to an additional pathology. Typically, CC changes are part of more diffuse white matter anomalies in temporal lobe epilepsy (TLE) [54–60], in frontal lobe epilepsy [61], in epilepsies due to different MCDs [8,42–44,50,52], in focal childhood epilepsies [53], and in idiopathic generalized epilepsy (IGE) syndromes [62,63]. Microstructural CC abnormalities were correlated to early onset of TLE [54,56] and to the presence of MCD [42,43,44]. These changes were considered seizure-induced and interpreted as Wallerian degeneration in TLE [58], in focal childhood epilepsy [53] and in epilepsies due to MCD [51]. There was no association with presence or absence of hippocampal sclerosis [59]. In TLE [60] and in IGE [61,62,63] microstructural CC changes were correlated to cognitive deficits. After resective epilepsy surgery for TLE, CC changes persisted [57], but did not affect the postsurgical outcome [55].

3. Role of CC in seizure spread

Since white matter structures include no firing neurons they cannot act as epileptic foci. Tükel and Jasper [64] were the first to describe secondary bilateral synchrony in parasagittal lesions. The cortical focus theory replaced the concept of primary generalized epilepsies [65]. CC and other interhemispheric connections were considered to transfer unilateral seizure activities to the contralateral hemisphere. MRI lesion mapping confirmed the genu of CC as the major pathway for seizure generalization [66]. An influence of CC in intra-hemispheric temporal coupling could also be demonstrated by electrocortical recordings [67].

4. Callosotomy as a treatment option

For multifocal or diffuse drug-resistant epilepsies - not amenable to resective epilepsy surgery – van Wagenen and Herren [68] suggested a role for callosal section. The extent includes anterior, posterior or total commissurotomy whether in a one-step or two-step procedure [69–74]. Radiosurgery has also been used [75–77].

Early and recent studies [72,78–81] concentrated on intractable generalized seizure types, especially tonic, atonic or mixed forms resulting in violent drops to the floor (termed "drop seizures" in this review). Secondarily generalized epilepsies [82], Lennox–Gastaut syndrome or Lennox-like syndromes [83,84], West syndrome [71,85] and intractable idiopathic generalized epilepsies [86,87] were included. PWE due to bihemispheric cortical dysplasias were also operated [88–91]. Common determinants were medical intractability of severe and disabling drop seizures in childhood. In one small series callosotomy was also performed in adults [92].

Preoperative EEG changes were in accordance with the selection of patients. Generalized spikes and waves, 2/s sharp and slow waves, runs of rapid spikes (Fig. 1), and generalized ictal patterns were recorded [73,83,84,93–95]. After commissurotomy, disruption of generalized discharges or their complete elimination was observed in the majority of patients [83,84,94,96,97]. In about half of patients, the postoperative EEG exhibited a unilateral spike focus (Fig. 2) [79,98]. No criteria in the preoperative EEG were known to predict outcome [93,99].

After callosotomy good to excellent improvement of drop seizures was reported [69,72,73,80–83,85,95]. Follow-up studies demonstrated a long-term effect [74,100–102]. Other generalized seizure types and partial seizures were improved to a lesser degree. Improvement in postoperative EEG was correlated with better seizure outcome [72,103]. Beside reduction of drop seizures positive changes in behavior, attention, overall daily and cognitive