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Partial agenesis of the corpus callosum in a patient with juvenile myoclonic epilepsy

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ABSTRACT – We describe a patient who presented at our epilepsy-monitoring unit with myoclonic jerks, and was diagnosed with juvenile myoclonic epilepsy (JME). Imaging of his brain revealed partial agenesis of the corpus callosum (ACC). We discuss the known genetic basis of both JME and ACC, as well as the role of the corpus callosum (CC) in primary generalized epilepsy. Both JME and ACC are associated with gene loci on chromosome 15q14. Structural brain abnormalities other than ACC, such as atrophy of the corpus callosum have been reported in patients with JME. ACC has been associated with seizures, suggesting an anti-epileptogenic role of the corpus callosum. On the other hand, corpus callosotomy is used to treat refractory idiopathic generalized epilepsy, which shows that the corpus callosum may play an epileptogenic role. The occurrence of both these conditions in one patient raises the question of whether they are purely coincidental or if there is a common basis for both. Several issues need to be addressed: the mechanism of seizure generalization in the setting of partial ACC, the possible role of other structures in generalization, and whether the ACC contributes to epileptogenesis as a result of the lack of a normal CC inhibitory effect.

Key words: agenesis, corpus callosum, juvenile myoclonic, epilepsy, genetics

Primary generalized seizures and generalized epileptiform activity are thought to require an intact corpus callosum. However, we were surprised to find that our patient, diagnosed with juvenile myoclonic epilepsy, had partial agenesis of the corpus callosum on brain MRI. We present our case and the known genetic basis of both syndromes, and we discuss the enigmatic role of the corpus callosum in epilepsy.

Case report

We present a 15-year-old, right-handed male who was referred to our epilepsy-monitoring unit with a two-month history of daily myoclonic jerks involving his shoulders, arms, and legs. Each episode lasted for 2-3 seconds, and did not cluster at any particular time of the day. There was no history of absence seizures. While there was no history of developmental delay, his family history was significant for epilepsy, with his mother presenting at age 22; she has generalized tonic-clonic seizures and is thought to have a primary generalized epilepsy. Her previous work-up was unavailable. A repeat EEG at age 45 was normal and she refused an MRI of the brain. She is on valproic acid and has

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been seizure-free for the last nine years. The patient had *in utero* exposure to carbamazepine, which his mother took, along with folic acid, during gestation. The patient has two brothers and one sister who are healthy. There was no consanguinity. The patient had no other risk factors for epilepsy such as head trauma or meningoencephalitis. His physical examination, including neurological assessment, was normal. Video-EEG monitoring revealed multiple interictal epileptiform discharges in the form of generalized polyspike bursts that were greater in amplitude over the left hemisphere than the right *(figure 1)*. Some of these were accompanied by visible clinical myoclonus. One event was followed by a generalized convulsion. The findings were consistent with a generalized epilepsy and suggested an idiopathic or primary generalized epilepsy (PGE) with myoclonus and generalized convulsions. The patient was diagnosed with juvenile myoclonic epilepsy (JME). He was treated with levetiracetam 500 mg twice daily and discharged home. Levetiracetam was chosen since it has been found to be effective and well tolerated in idiopathic generalized epilepsies including JME (Di Bonaventura *et al.* 2005). A 3-Tesla MRI of the brain showed partial agenesis of the corpus callosum (ACC) and colpocephaly (*figure 2)*. He was seizure-free three months following discharge.

Discussion

ACC is a developmental disorder, the precise prevalence of which is unknown. An incidence of 1.6% for partial or complete ACC was reported in a review of 445 consecutive pediatric MR scans (Bodensteiner *et al.* 1994). Clinical symptoms vary and many patients are asymptomatic. While ACC may occur in isolation, it has been associated with over 20 developmental syndromes (Bedeschi *et al.* 2006). In one study, 35% of patients with ACC presented with epilepsy, and all of them prior to eight years of age. Partial seizures were most common. There is a paucity of literature associating ACC with primary generalized epilepsy such as JME.

JME is a primary generalized epilepsy syndrome that has a frequency of 0.5-1 per thousand. Several structural abnormalities of the brain have been described in patients with JME including abnormalities of ventricular size, arachnoid cysts, cortical and brainstem atrophy, and cavum septum

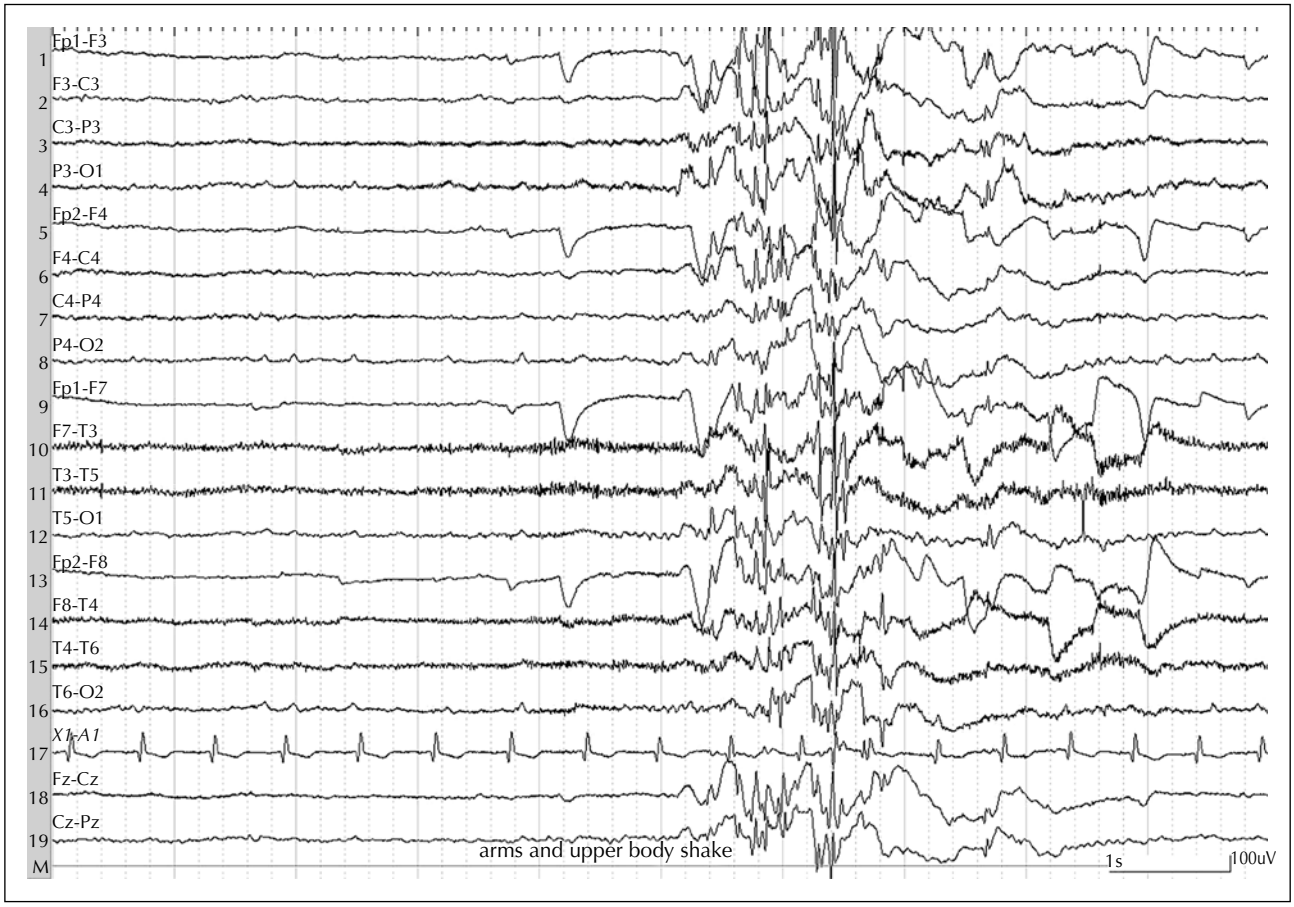

Figure 1. Generalized polyspike discharge.

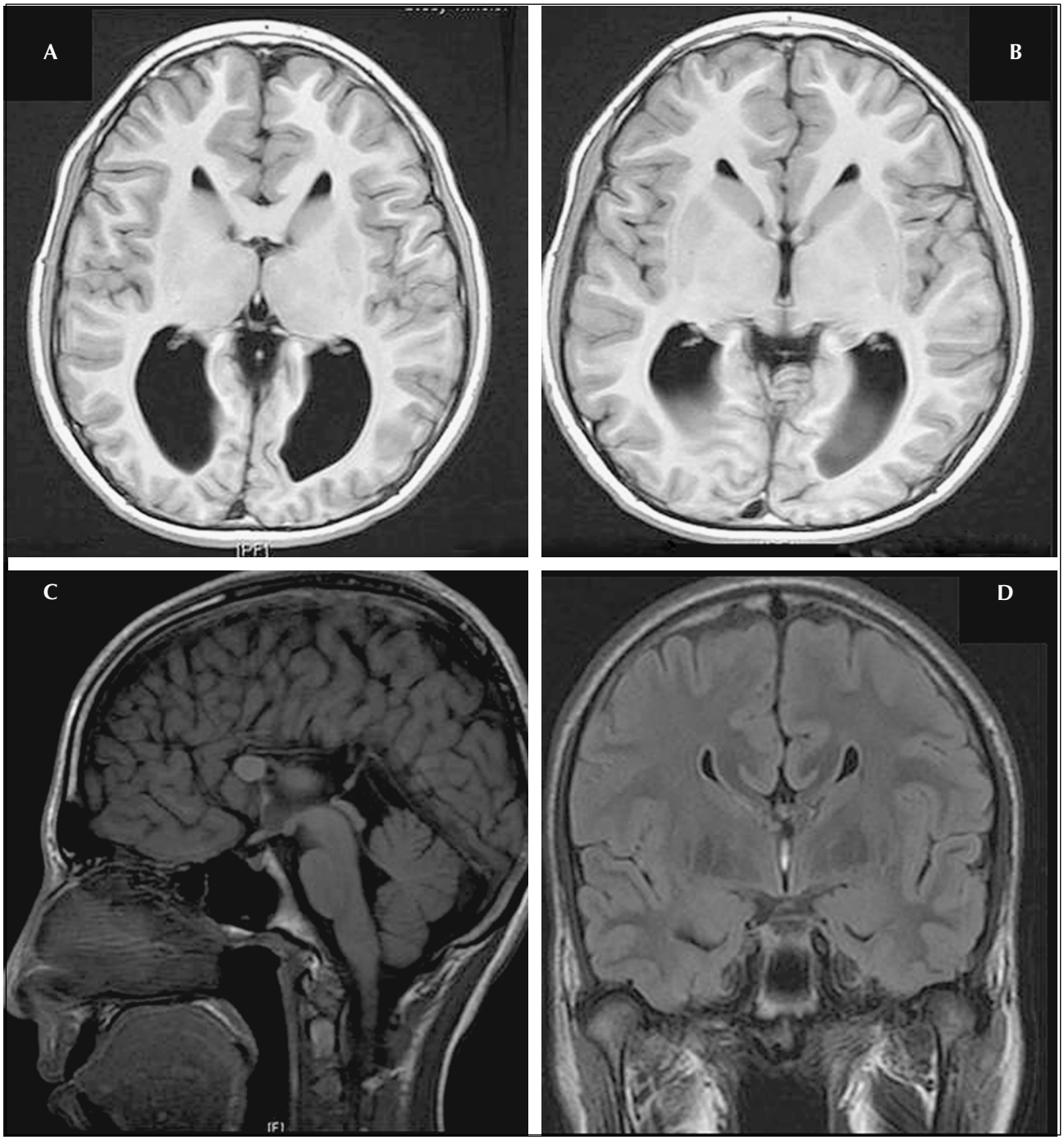

Figure 2. Three-Tesla MRI of brain with axial (**A, B**) sagittal (**C**) and coronal (**D**) views.

pellucidum (Gelisse *et al.* 2000). A recent study showed the presence of atrophy of the corpus callosum in patients with JME (Tae *et al.* 2006). However, ACC has not been reported in the setting of JME. Knowing the incidence of both JME and ACC, the probability of both conditions occurring by chance in the same patient is estimated to be 1 in 62,500.

Significant progress has been made in understanding the genetics of both syndromes. JME has been associated with gene loci on chromosomes 6p and 15q14. A recent study provided confirmatory evidence for an allelic and genotypic association of the connexin 36 (CX36) gene on 15q14 with JME (Hempelmann *et al.* 2006). In addition, the region on 15q14 encompassing the KCC3 gene has

been linked to both JME and a syndrome involving ACC (Mercado *et al.* 2004). The latter syndrome consists of a peripheral neuropathy with or without agenesis of corpus callosum (ACCPN). The gene locus for ACCPN lies in a region of 2cM between markers D15S1040 and ACTC on 15q14. Eleven genes have been positioned within this interval, including KCC3 and CX36 (Howard *et al.* 2002). Whether our patient has a gene mutation at 15q14 leading to JME and ACC is an unanswered question since he did not consent to genetic testing.

The role of the corpus callosum (CC) in epilepsy seems paradoxical. In general, the CC is considered to be an essential structure in seizure generalization. For that reason, corpus callosotomy (particularly of the anterior two-thirds) is an important surgical option for patients with severe refractory generalized epilepsy. There are data suggesting a reduction of both primary and generalized seizures with callosotomy (Spencer *et al.* 1993). The amount of corpus callosum needed for generalization to occur is not clear. It has been found that resection of the anterior two-thirds of the corpus callosum is sufficient to achieve significant improvement in seizure control. For patients who fail to improve after anterior section, total section of the corpus callosum showed cure or marked diminution of various seizure types suggesting an incremental response (Spencer *et al.* 1993). It has been noted that the role of the CC in PGE is probably more than just a passive conduit of cortical seizure activity from one hemisphere to the other. With direct intraoperative monitoring of the compound CC potential, it was discovered that CC neural firing *preceded* the cortical spike by over 100 ms (Wada 2005), suggesting that the CC may play an active role in PGE epileptogenesis.

However, there is also a body of evidence to suggest that the intact CC may have an inhibitory role in epilepsy, particularly with regard to focal epilepsy. For example, it has been observed that seizures may worsen following callosotomy (Spencer *et al.* 1993, Wada 2005). In primates with transected CC, kindling and ictal march has been observed to proceed more rapidly. In monkeys, corpus callosum bisection markedly intensified lateralized ALOH focus-onset seizures, driving it to fatal status epilepticus (Wada 2005). This may be due to elimination of mutually inhibitory effects of asymmetrically located foci. It is unclear whether the inhibitory effect is directly from the CC, or a propagation of an inhibitory effect of the intact contralateral hemisphere. In addition, some lesions of the CC, such as a CC lipoma, are associated with generalized seizures, suggesting the removal of an inhibitory effect. Corpus callosum lipoma may itself cause seizures due to infiltration of the neural substance by the dense fibrous tissue of the capsule. This progressive fibrosis may be comparable to a scar, and the mechanism may be similar to that associated with scarring found in post-traumatic epilepsy. Generalized seizures and bilateral synchronous discharges may persist following total callosotomy. These may be due to either surgical scarring or involvement of other structures (such as the diencephalon), which may play a role in epileptogenesis.

Several questions arise given the coincidental occurrence of a PGE and a malformation of the CC in our patient. For example, how are the generalized seizures occurring, in light of the partial ACC? Are seizures and generalized epileptiform discharges being propagated (or even originating) exclusively via the intact anterior portion of the CC, or are other midline structures such as the brainstem or diencephalon involved? Is the ACC contributing to epileptogenesis via a deficiency of the normal CC inhibitory effect? Is there any common genetic basis in this patient? The relationship between ACC and epilepsy in this patient is unclear and emphasizes the need for further research. □

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