Agenesis of the corpus callosum

What is a callosal disorder?
Disorders of the corpus callosum are conditions in which the corpus callosum does not develop in a typical manner. Since these are disorders of brain structure, they can only be diagnosed by brain scan, including:

- Pre/postnatal sonogram (ultrasound)
- Computerized axial tomography (CT-scan or CAT scan)
- Magnetic resonance imaging (MRI)

The disruptions to the development of the corpus callosum occur during the 5th to 16th week of pregnancy. There is no single cause and many different factors can interfere with this development, including:

- Prenatal infections or viruses (for example, rubella)
- Chromosomal (genetic) abnormalities (for example, trisomy 8 and 18, Andermann syndrome, and Aicardi syndrome)
- Toxic metabolic conditions (for example, Fetal Alcohol Syndrome)
- Blockage of the growth of the corpus callosum (for example, cysts)

Disorders of the corpus callosum are not illnesses or diseases, but abnormalities of brain structure. Many people with these conditions are healthy. However, other individuals with disorders of the corpus callosum do require medical intervention due to seizures and/or other medical problems they have in addition to the disorder of the corpus callosum.

Estimates of the frequency of corpus callosum disorders (particularly agenesis of the corpus callosum or ACC) vary greatly. Some suggest as many as 7 in 1000 children may have ACC, while others believe it may be as rare as 5 in a million. The rate of diagnosis of these disorders is likely to increase with greater access to the brain scanning technology listed above.

What is the corpus callosum?
The corpus callosum is the largest connective pathway in a human brain. It is made of more than 200 million nerve fibers that connect the left and right sides (hemispheres) of the brain.

If we cut a brain in half down the middle, we would also cut through the fibers of the corpus callosum. When looking at the middle side of one half of the brain, for example, in magnetic resonance imaging (MRI), the corpus callosum looks like a cross-section of a mushroom cap at the center of the brain.

Each hemisphere of the brain is specialized to control movement and feeling in the opposite half of the body, and each hemisphere specializes in processing certain types of information (such as language or spatial patterns). Thus, to coordinate movement or to think about complex information, the hemispheres must communicate with each other. The corpus callosum is the main connector that allows that communication.

In a typical infant brain, the corpus callosum develops between 12 to 16 weeks after conception (near the end of the
first trimester). While the entire structure develops prior to birth, the fibers of the corpus callosum continue to become more and more effective and efficient on into adolescence. By the time a child is approximately 12 years of age, the corpus callosum functions essentially as it will in adulthood, allowing rapid interaction between the two sides of the brain. From this age on (and typically earlier) as the corpus callosum becomes increasingly functional in their typically developing peers, children with ACC appear to fall behind developmentally because the corpus callosum is absent.

Parents often ask if the corpus callosum is the only path between the hemispheres of the brain. It isn’t the only path, but it is by far the most important. Some much smaller connections are usually present in ACC. The anterior commissure is the largest and most useful of these other pathways. However, it only has about 50,000 nerve fibers, a far cry from the more than 200 million fibers in the corpus callosum.

Diagnoses
The following sections clarify the differences between complete agenesis of the corpus callosum (ACC), partial ACC, hypoplasia of the corpus callosum, and dysgenesis of the corpus callosum.

Complete agenesis of the corpus callosum. If the nerve fibers don’t cross between the hemispheres during that critical prenatal time, they never will. ACC becomes a permanent feature of the individual’s brain. The callosal fibers may have started to grow, but when unable to cross between the hemispheres, they grow toward the back of the same hemisphere where they began. These fibers form what are called Bundles of Probst. Some smaller connections between the hemispheres develop in most individuals with ACC. These are the anterior commissure, posterior commissure, and hippocampal commissure. However, each of these is at least 40,000 times smaller than the corpus callosum. Thus, they cannot compensate completely for the absence of the corpus callosum.

Partial agenesis of the corpus callosum. In partial ACC, the corpus callosum began to develop, but something stopped it from continuing. Since the corpus callosum develops from front to back, the part of the corpus callosum that is present in partial ACC usually will be toward the front of the brain, with the back portion missing. Partial ACC includes the entire range of partial absence, from absence of only a small portion of callosal fibers to absence of most of the corpus callosum. In partial ACC, the other smaller commissures usually are present.

Hypoplasia of the corpus callosum. Hypoplasia refers to a thin corpus callosum. On a mid-line view of the brain, the structure may extend through the entire area front-to-back as would a typical corpus callosum, but it looks notably thinner. It is unclear in this case if the callosal nerve fibers are fully functional and just limited in number, or if they are both less plentiful and more dysfunctional.

Dysgenesis of the corpus callosum. Dysgenesis means that the corpus callosum developed, but developed in some incomplete or malformed way. Thus, partial ACC and hypoplasia of the corpus callosum would be forms of dysgenesis, as would any other form of inadequate callosal development. Dysgenesis is a broad term for any malformation of the corpus callosum that is not a complete absence (agenesis).

Characteristics
Physically, complete ACC is a condition that does not change. It will not get worse. Since the corpus callosum is already absent, it cannot regenerate or degenerate. Likewise, in partial ACC and hypoplasia, once the infant’s brain is developed, no new callosal fibers will emerge.

In that sense, disorders of the corpus callosum are conditions one must “learn to live with” rather than “hope to recover from.” Long-term challenges are associated with malformation of the corpus callosum, but this in no way suggests that individuals with DCC cannot lead productive and meaningful lives.

What are the common developmental problems that may occur with disorders of the corpus callosum?
Behaviorally individuals with DCC may fall behind their peers in social and problem solving skills in elementary school or as they approach adolescence. In typical development, the fibers of the corpus callosum become more efficient as children approach adolescence. At that point children with an intact corpus callosum show rapid gains in abstract reasoning, problem solving, and social comprehension. Although a child with DCC may have kept up with his or her peers until this age, as the peer-group begins to make use of an increasingly efficient corpus callosum, the child with DCC falls behind in mental and social functioning. In this way, the behavioral challenges for individuals with DCC may become more evident as they grow into adolescence and young adulthood.

Behavioral characteristics related to DCC
This is an overview of the behavioral characteristics which are often evident in individuals with DCC.

- Delays in attaining developmental milestones (for example, walking, talking, reading). Delays may range from very subtle to highly significant.
- Clumsiness and poor motor coordination, particularly on skills that require coordination of left and right hands and feet (for example, swimming, bike riding, tying shoes, driving).
- Atypical sensitivity to particular sensory cues (for example, food textures, certain types of touch) but often with a high tolerance to pain.
- Difficulties on multidimensional tasks, such as using language in social situations (for example, jokes, metaphors), appropriate motor responses to visual information (for example, stepping on others' toes, handwriting runs off the page), and the use of complex reasoning, creativity and problem solving (for example, coping with math and science requirements in middle school and high school, budgeting).
- Challenges with social interactions due to difficulty imagining potential consequences of behavior, being insensitive to the thoughts and feelings of others, and misunderstanding social cues (for example, being vulnerable to suggestion, gullible, and not recognizing emotions communicated by tone of voice).
- Mental and social processing problems become more apparent with age, with problems particularly evident from junior high school into adulthood.
- Limited insight into their own behavior, social problems, and mental challenges.

These symptoms occur in various combinations and severity. In many cases, they are attributed incorrectly to one or more of the following: personality traits, poor parenting, ADHD, Asperger's Syndrome, Nonverbal Learning Disability, specific learning disabilities, or psychiatric disorders. It is critical to note that these alternative conditions are diagnosed through behavioral observation. In contrast, DCC is a definite structural abnormality of the brain diagnosed by an MRI. These alternative behavioral diagnoses may, in some cases, represent a reasonable description of the behavior of a person with DCC. However, they misrepresent the cause of the behavior.

**Frequently asked questions**

**Can DCC be cured?**

Stem-cell research has raised expectations and hopes that we may find “cures” for some forms of nervous system damage and developmental abnormalities. At this time, it does not seem likely that DCC will be impacted by such interventions. This is due to the large number of steps in the process of development of the corpus callosum that would need to be re-instituted. Another factor is that the brain already has organized without the corpus callosum. Overall, disorders of the corpus callosum are conditions one must “learn to live with” rather than “hope to recover from.” Long-term challenges are associated with absence of the corpus callosum, but this in no way suggests that individuals with DCC cannot lead productive and meaningful lives.

**What is the difference between structural diagnosis vs. behavioral syndromes?**

DCC are physical diagnoses based solely on an anatomical reality, the absence of the corpus callosum. This does not mean that DCC do not have behavioral characteristics, they clearly do. However, DCC is not a “behavioral” diagnosis such as Attention Deficit Hyperactivity Disorder (ADHD), Non-Verbal Learning Disability, Autism, or Asperger’s Syndrome. In contrast to DCC, these syndromes are diagnosed strictly based on unusual or abnormal behaviors. Although much research has been done, it is not clear what, if anything, is structurally wrong with the brain in most of these disorders. On the other hand, the diagnosis of DCC is clear and unambiguous. Once an embryo passes the 16th week, if the corpus callosum isn’t there, the diagnosis is permanent. At this point, the absence of the corpus callosum is visibly evident on brain scans.

**Who can diagnose ACC?**

ACC/DCC must be diagnosed by viewing the brain, either with MRI, Computerized Axial Tomography (CT-scan or CAT scan), or pre/post-natal sonogram (ultrasound). Among these, MRI is clearly best to see DCC and any other brain abnormalities. Absence of the corpus callosum can be seen at any age after the critical period of prenatal development. A neurologist or other physician may request an MRI or CT scan of the brain. An obstetrician or neonatal specialist may request an extensive pre-natal or post-natal sonogram or MRI. The pictures typically will be examined by a neuroradiologist or pediatric neuroradiologist, who will write a report describing any unusual findings. A neurologist or other physician also may examine the scan and diagnose ACC. If that is the case, it is always wise to have a neuroradiologist re-examine the pictures to verify the diagnosis and carefully assess for any other possible abnormalities. DCC itself cannot be detected by amniocentesis.
What causes ACC?
ACC/DCC does not have a single cause. In fact, there are multiple factors that may be involved in disrupting the formation of the corpus callosum. Among the suggested causal factors are genetics, metabolic disorders, and structural interruptions. Brain cells may not get the chemical guidance needed to grow in the right direction, possibly because of a faulty gene. Similarly, the nerve cells may not reach their destination due to lack of oxygen, poor nutrition, toxic chemicals (for example, alcohol or drugs), infections, or metabolic disturbance. Finally, the development of the corpus callosum may be stopped by some other developmental process that interrupts the initial crossing-point of callosal fibers. In these individuals, DCC may be accompanied by cysts or lipomas. There are no known medical conditions in which DCC is always present.

Some of the conditions in which DCC is usually present are: Aicardi Syndrome, Shapiro Syndrome, Acrocallosal Syndrome, Mowat-Wilson Syndrome, and Toriello Carey Syndrome.

Some of the conditions in which DCC is sometimes present are: Fetal Alcohol Syndrome, intra-uterine infections, maternal riboflavin/ folate/ or niacin deficiency, Dandy-Walker Syndrome, Andermann Syndrome, Arnold-Chiari II Malformation, Holoprosencephaly, Hirschsprung Disease, Occulo-Cerebro-Cutaneous Syndrome, Menkes Disease, Hydrocephalus, and others.

Will DCC get worse?
Physically, complete ACC is a condition that does not change. It will not get worse. Since the corpus callosum is already absent, it cannot regenerate or degenerate. Likewise, in partial ACC and hypoplasia, once the infant’s brain is developed, no new callosal fibers will emerge.

Behaviorally, however, individuals with ACC/DCC may fall behind their peers in social and problem solving skills in elementary school or as they approach adolescence. In typical development, the fibers of the corpus callosum become more efficient as children approach adolescence. At that point children with an intact corpus callosum show rapid gains in abstract reasoning, problem solving, and social comprehension. Although a child with DCC may have kept up with his or her peers until this age, as the peer-group begins to make use of an increasingly efficient corpus callosum, the child with DCC falls behind in mental and social functioning. In this way, the behavioral challenges for individuals with DCC may become more evident as they grow older.

Why does my child have ACC?
Many parents worry that they may have caused their child to have brain damage or may fear that it is a condition that will recur in future children. In addressing those questions, it is important to remember that it is usually impossible to establish the reason a particular child has DCC.

Genetic testing may reveal a genetic abnormality or syndrome that is the underlying cause of the DCC. In these cases, the parents or the individual with DCC will want to consult a genetic counselor prior to becoming pregnant with another child. In the absence of an identified genetic abnormality, it is extremely difficult to find a specific cause of DCC. Multiple possible causes appear to exist, and genetic testing does not always reveal what that cause might be. If it is not genetic, it was caused by something that happened during the first trimester of pregnancy. While it is understandable that parents will want to know "why this happened," in many cases they may never know. Therefore it may be important to shift the focus from asking "why?" to asking "what can we do to cope with the diagnosis?" and "how can we best help our child?"

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