AGENESIS OF THE CORPUS CALLOSUM

Information for families affected by Disorders of the Corpus Callosum

Corpal

DCC & Aicardi Syndrome UK

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Being told your child has agenesis or dysgenesis of the corpus callosum can be distressing news. The major pathway that connects the two halves of the brain has failed to form correctly before birth; what will this mean for the development of your child? You may be told that this depends on whether there are other brain malformations, or whether the abnormality has been caused by a specific genetic mutation. However, often a genetic cause is not found with diagnostic tests, and even if a genetic cause is found, it may not give a lot of information about how your child will function in the future.

This booklet has been written for families when they find out their child has a disorder of the corpus callosum, such as agenesis (not forming) or dysgenesis (forming abnormally). The diagnosis may have been given before birth during a routine antenatal ultrasound scan or following an MRI scan, or after birth following an MRI or a CT scan of the brain. The information contained within this booklet may also be of interest to individuals who have been told later in life that they themselves have a disorder of the corpus callosum. This may have been discovered as an incidental finding during a routine brain scan, or during an investigation for another condition, such as epilepsy.

The booklet has been written in consultation with various medical professionals such as neurologists and paediatricians, and research scientists who have an interest in how the corpus callosum forms in the brain and what happens when it fails to develop. It aims to bring together what is currently known about the condition, how it might be caused, what the possible range of outcomes might be, and what support is available. It is hoped that this booklet will go some way towards answering some of the many questions families naturally ask when a disorder of the corpus callosum is detected. Also, to provide some background to why the condition can lead to such a wide range of outcomes, which are currently difficult to predict.

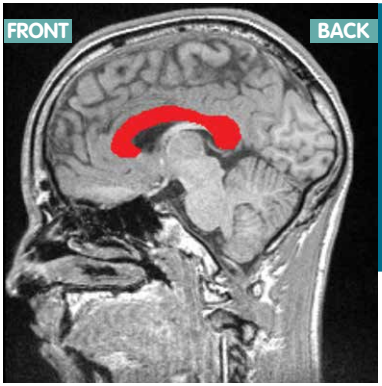
The booklet has been developed with the help of families who have a child with a disorder of the corpus callosum and contains information that they felt would be useful to know. Topics are covered that they would have liked to have known about in the early days of finding out about their child's condition, or that they would have found helpful when working with professionals with less knowledge of this condition.

Until recently, our knowledge of the outcome in individuals with disorders of the corpus callosum was derived largely from individuals who had come to clinics because of significant difficulties. However, with advances in neuroimaging and prenatal ultrasound, disorders of the corpus callosum are now more often diagnosed before birth, or incidentally after birth. This has led to a rapid increase in information about the condition and range of outcomes. There is an almost overwhelming amount of information available online, and this booklet aims to summarise it succinctly and clearly.

What is the corpus callosum?

The two sides (hemispheres) of our brains are connected by a thick bundle of nerve fibres called the corpus callosum.

Although each brain hemisphere looks identical in shape and size, they are not exactly the same and perform different functions. The left hemisphere is generally in charge of movement of the right side of the body, and in turn, the right hemisphere controls the left side of the body. Different areas of the brain also become specialised for different functions as the brain develops. For example, for many people the left hemisphere is responsible for language, calculations and logical abilities; while the right hemisphere is involved in understanding spatial relationships, visual imagery and, some say, creativity. While this is a simplified view of how our brain functions and there is variation between people, the two hemispheres of the brain work together and share information through the corpus callosum.



The corpus callosum is the largest and most easily visible connection in the human brain and allows neural messages to be transferred across the two halves of the brain

An MRI through the middle of a typical brain with the corpus callosum in red.

The corpus callosum is a thick bundle of nerve fibres that connects the two sides (hemispheres) of our brains

How does the corpus callosum develop?

The corpus callosum starts to form very early in human life. From around the 6th week of pregnancy, nerve fibres (or *axons*) that are destined to cross from one side of the brain to the other can be seen growing. From the 12th week, these nerve fibres approach the midline and receive cues to cross over to the other side of the brain to form the corpus callosum. The front sections of the corpus callosum begin to grow from the 14th week; the back sections begin to grow from the 18th week. The shape of the corpus callosum is complete at around the 20th week, although the nerve fibres continue to grow and expand during pregnancy, and up to 2 months after birth. During this time, many other brain structures also continue to grow and develop.

The corpus callosum is formed during the first half of pregnancy and is made up of over 200 million nerve fibres

A fully formed corpus callosum is made up of over 200 million nerve fibres and this number is fixed from birth. However, the shape and volume of the corpus callosum changes throughout childhood and adolescence due to the adjustment and fine-tuning of connections.

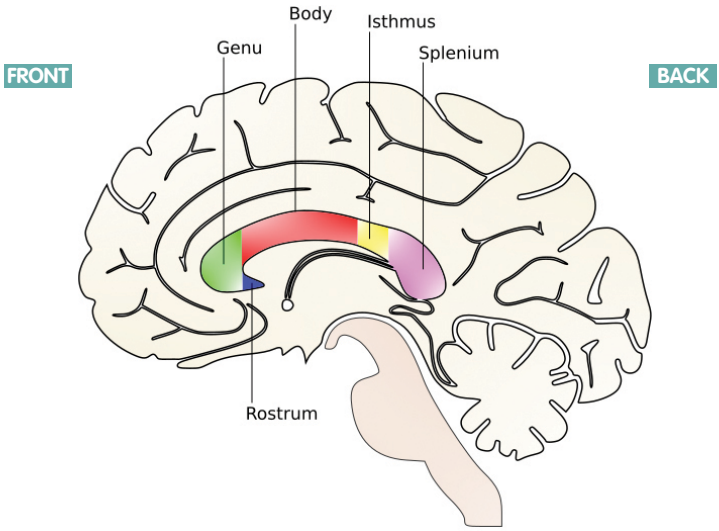
From around 3 months of age, the nerve fibres become covered with an insulating coat (made of myelin), which helps information travel faster between brain areas. The myelin coat makes the corpus callosum expand in size further until its shape resembles that of an adult. There is also some fine-tuning of the connections between nerve fibres, during which new connections form and other connections are removed. This fine-tuning leads to our brains becoming more able to process information quickly and efficiently as we develop.

The nerve fibres of the corpus callosum are insulated in a protective coat made of myelin

After birth, connections between nerve fibres are fine-tuned

Our brains, and therefore our corpus callosum, continue to grow during childhood and adolescence as they become more effective and efficient. The eventual size and shape of the corpus callosum can vary between individuals; in a typical adult brain, the corpus callosum is around 10 centimetres in length as measured from the front of the brain to the back.

Although there are no clear landmarks to subdivide the corpus callosum it is often considered in four main segments. The front portion is the *genu*, and this curves around and forms the *rostrum* underneath. Moving towards the back of the brain, it becomes the *body*, and ends with the *splenium*. The *isthmus* is the narrowest part of the body, in front of the splenium. In terms of timing, the development of the genu and the body occurs before that of the splenium and rostrum. Each segment connects distinct areas of the brain and is involved in coordinating different functions such as movement, sound and vision.



The different segments of the corpus callosum shown through the middle of a typical brain

Are there other connections between the two halves of the brain?

The corpus callosum is not the only connection between the left and right hemispheres of the brain, but it is the largest and most important one. Other connections (*commissures*) also exist, allowing nerve fibres to cross between the hemispheres. One of these is the *anterior commissure*, which can be found near the front and base of the brain and consists of around 50,000 nerve fibres. The anterior commissure develops independently from the corpus callosum and forms early in development (from around the 7th week of pregnancy).

Other main connections between the left and right hemispheres include the posterior, hippocampal and habenular commissures located near the back and base of the brain. None of these commissures contain nearly as many fibres as the corpus callosum; they can be considered like small roads compared to the major motorway that is the corpus callosum. They may be present or absent in individuals with agenesis of the corpus callosum.

What is the role of the corpus callosum?

The primary function of the corpus callosum (and the commissures) is to transfer information back and forth between the two brain hemispheres. Different areas of the brain are constantly in communication with each other and the corpus callosum facilitates this by integrating sensory, motor and cognitive information originating from the two sides of the brain. Having two hemispheres work together in a co-ordinated fashion allows more efficient processing of complex information.

The connections in the corpus callosum allow information to be shared between the hemispheres (excitatory) and allow areas in the right and left hemispheres to inhibit or withhold each other in order to function one at a time (inhibitory). This may reduce non-essential processing between the hemispheres and allow the brain to process information more efficiently.

As the brain develops, the corpus callosum is thought to enable the specialisation of brain areas for different cognitive functions; for example, the specialisation of language in the left hemisphere and spatial awareness in the right hemisphere.

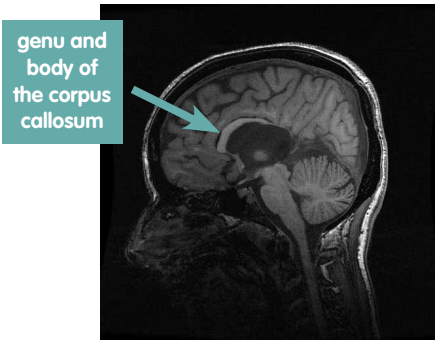
What is agenesis of the corpus callosum?

Agenesis of the corpus callosum describes the condition in which the corpus callosum failed to develop, either partially or completely. In *complete agenesis*, the corpus callosum is completely absent and did not develop. In *partial agenesis* (also referred to as *hypogenesis*), the corpus callosum began to develop, but something stopped it from growing in the usual way. As the corpus callosum generally develops from front to back, the part of the corpus callosum present is usually at the front, but this is not always the case. A small portion of the corpus callosum may remain, or it could be present but smaller and thinner than usual.

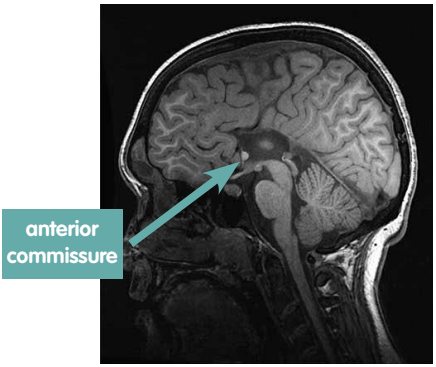
If all of the corpus callosum forms, but it is unusually thin, this may be referred to as *hypoplasia* of the corpus callosum. It is not clear whether the nerve fibres in a thin corpus callosum will be fully functional and just fewer in number, or whether they are both dysfunctional and limited in number. Another rare condition is *hyperplasia*, which describes an unusual thickening of the corpus callosum.

If the corpus callosum developed, but is malformed or incomplete in some way, it can be described under the broad term *dysgenesis of the corpus callosum*. Complete agenesis, partial agenesis, hypoplasia, and dysgenesis all come under the umbrella term *disorders of the corpus callosum*.

THE CORPUS CALLOSUM



MRI image showing **partial absence of the corpus callosum**. The genu and body of the corpus callosum are present. The splenium is absent.



MRI image showing **complete absence of the corpus callosum**. The anterior commissure is present and larger than normal.

Agenesis - failure to grow; implying that the corpus callosum is absent

Dysgenesis - corpus callosum is present but is malformed in some way; e.g., too small, misshapen, or with a part missing

Hypogenesis - incomplete formation; can be used to describe partial agenesis of the corpus callosum

Hypoplasia - underdevelopment; the corpus callosum may be complete, but is thinner than usual

Hyperplasia - thickening of the corpus callosum, which may result from reduced axonal pruning after birth

Can the corpus callosum grow back?

Parents often ask whether the corpus callosum will grow back at some point, or if it might grow later on in pregnancy. It is important to understand that if the corpus callosum does not form during the critical time for development in prenatal life (that is, by the 20th week of pregnancy), then it never will. Similarly, if only part of the corpus callosum is formed, no new fibres will emerge. The amount of nerve fibres crossing the hemispheres is fully established by birth, or soon after. However, the fibres of the corpus callosum that are present will change in size and shape as the brain grows. In the case of partial agenesis of the corpus callosum, the existing fibres of the corpus callosum will continue to develop throughout childhood and adolescence.

What happens in the brain when the corpus callosum does not develop?

As the largest connective pathway in the brain, the corpus callosum is said to be a critical structure. The brain, however, has an extraordinary capacity to cope with differences, change and damage; this is referred to as *neural plasticity*. The brain can therefore compensate to some degree when the corpus callosum has failed to develop. The use of modern neuroimaging techniques has enabled researchers to study the rewiring of the neural connections in people with disorders of the corpus callosum and see how these connections differ from typically developed brains. Although there may be compensatory or alternative pathways, these are unlikely to be as efficient as a typically formed corpus callosum. Disorders of the corpus callosum are sometimes associated with other malformations in the brain and these are also likely to further impact the overall functioning of the brain.

In some people with agenesis of the corpus callosum, the nerve fibres that were destined to cross between the two hemispheres follow a different route. Instead of crossing between the hemispheres, the nerve fibres grow toward the front and back of the same hemisphere where they began. These bundles of rerouted fibres are known as *Probst bundles*. Researchers studying the function of Probst bundles think these nerve fibres may still play a role in connecting brain regions and transferring information.

The plasticity of the developing brain can result in the formation of new connections in the absence of the corpus callosum

Even when the corpus callosum has failed to develop completely, the smaller connections between the two hemispheres are often still present. These commissures may also be affected by the disruption in development and be smaller than normal; alternatively, they can also be enlarged. Researchers suggest this enlargement could indicate some compensation has been made for the absence of the corpus callosum during development. While these commissures allow information to be transferred between the hemispheres, they do not have the same level of functionality as the corpus callosum.

How does agenesis of the corpus callosum differ to 'split-brain' patients?

Much of what we know about the role of the corpus callosum comes from the study of patients with severe epilepsy who had their (normally formed) corpus callosum surgically cut to stop the spread of seizures throughout the brain. This surgical procedure is able to alleviate life-threatening epileptic seizures and generally has little impact on everyday functioning. However, as the two hemispheres are no longer able to exchange information as efficiently as before, each hemisphere can appear to act independently. For example, information such as words, pictures and objects presented to one hemisphere, can go unnoticed by the other.

Individuals with agenesis of the corpus callosum, by contrast, do not tend to show this level of disconnection seen in these so-called 'split-brain' patients who have had their corpus callosum surgically cut. Although agenesis of the corpus callosum has been referred to as a 'natural split-brain' – how the brain develops and reorganises itself in the absence of the corpus callosum is very different to when this disconnection is made later in life. Researchers report that information can be integrated in the brain using alternative pathways, but this process may take longer, particularly for complex information.

How common are disorders of the corpus callosum?

While rare, agenesis of the corpus callosum is one of the more common brain malformations present at birth. Recent estimates suggest that at least 1 in every 4,000 individuals may have agenesis of the corpus callosum (either partial or complete). However, this estimate was based on the diagnosis being made within the first year of life. As the condition can be identified at a later age, researchers suggest incidence rates may be closer to **1 in every 3,000 individuals**.

This rate could still be an underestimate as mild cases of the condition may go undetected. We know that some people learn about their brain difference as an incidental finding following a routine MRI or CT scan for medical or research reasons. We therefore do not know the true incidence unless population-wide scanning studies are conducted to examine this.

It has been questioned whether the number of people with disorders of the corpus callosum is increasing. It is likely that detection rates are increasing, rather than the condition itself. Brain scanning has become more accessible in recent years. Scanning methods used during pregnancy are also more sophisticated, meaning abnormalities in the fetal brain are more likely to be found.

It is widely acknowledged that abnormalities in the formation of the corpus callosum are more common in individuals with neurodevelopmental disabilities and known genetic conditions. Studies have found that 3 to 5% of individuals with learning disabilities can also have agenesis of the corpus callosum.

How are disorders of the corpus callosum detected?

Disorders of the corpus callosum can only be diagnosed by performing a scan of the brain. It is defined by a structural difference and not by differences in brain function or behaviour. It therefore differs to many neurodevelopmental disorders that are currently diagnosed based on behaviour (and where brain imaging may look normal) such as autism, attention deficit hyperactivity disorder and dyslexia.

The corpus callosum is most reliably seen from 20 weeks of pregnancy on an ultrasound scan. For many families, abnormalities in the corpus callosum are picked up during the routine ultrasound scan around this time. However, making a diagnosis at this point can be challenging; the brain has not fully developed and it can be difficult to visualise the corpus callosum and reliably determine the extent of any abnormality (e.g., whether it is completely or partially absent, thinner or just shorter than normal). Often the diagnosis is first suspected due to the presence of other features that are secondary to the malformation of the corpus callosum, such as enlargement of the fluid filled spaces (ventricles) in the brain (referred to as *colpocephaly*), absence of a specific small cavity (*cavum septum pellucidum*), or the widening of the deep groove that separates the two hemispheres (*interhemispheric fissure*).

As pregnancy progresses, the brain develops further and more detail can be seen on an ultrasound scan. An MRI scan may be suggested at this time to confirm the ultrasound findings, or later on in pregnancy (with the third trimester usually the optimal time to assess ongoing development of other areas of the brain). An MRI scan may also be suggested soon after birth, to help confirm the diagnosis and identify whether any associated brain problems are present.

Not all disorders of the corpus callosum are detected before birth and for many people they are identified only when they receive a brain scan for some other reason. This may be during childhood because of developmental concerns or neurological symptoms (e.g. epilepsy). Or it may not be discovered until later in life during a routine scan conducted for clinical (e.g. following a head injury) or research purposes.

Corpus callosum disorders can only be diagnosed by brain imaging using one or more of the following scanning procedures:

Ultrasound imaging (sonography) uses high-frequency sound waves to outline structures within the body. A transducer, placed on the skin, sends out pulses of ultrasound into the body; the sound waves echo or bounce back off dense surfaces and by timing these returning echoes, an image of internal structures can be formed.

Computerised axial tomography scan (CT-scan or CAT scan) is a combination of multiple X-rays taken at different angles; these are analysed by a computer to produce a detailed three-dimensional image of structures inside the body. This differs from an X-ray machine, which sends just one radiation beam; the CT-scan produces a more detailed final picture than an X-ray image. A CT-scan may not be recommended during pregnancy due to the exposure to radiation.

Magnetic resonance imaging (MRI) uses strong magnetic fields and radio waves to create detailed images of the organs and tissues within the body. MRI scans can produce very high-resolution images and unlike X-rays and CT-scans, they do not use radiation and is therefore considered safe in pregnancy.

More sophisticated MRI scans are now available, such as *diffusion tensor imaging (DTI)* and *diffusion weighted image (DWI)*, which can assess the integrity of the existing connecting fibres in the brain and are sensitive methods to visualise white matter changes or differences.

What is an 'isolated finding'?

A diagnosis of *isolated* agenesis of the corpus callosum is made if no additional brain abnormalities are seen on brain imaging. By contrast, *complex* or 'syndromic' agenesis of the corpus callosum are terms used by clinicians when there are additional, complex alterations of brain (or sometimes even whole body) structures.

How accurate are prenatal scans for diagnosing disorders of the corpus callosum?

Although prenatal imaging methods have become more advanced in recent years, some malformations in the brain can be missed during screening, or may be incorrectly identified when no abnormality is actually present, and some uncertainty may remain. The accuracy of the diagnosis increases when ultrasound is used in combination with a detailed MRI scan.

Structural abnormalities not detected during pregnancy may become apparent only when scans are conducted after birth. Of note, a recent review found 15% of cases that were thought to be *isolated instances of agenesis of the corpus callosum* when examined during pregnancy, were found to have additional *associated abnormalities* after birth. Prenatal imaging is therefore not always able to differentiate between complex and isolated forms of callosal disorders. Postnatal imaging and a thorough clinical examination are therefore necessary to confirm that agenesis of the corpus callosum is truly isolated.

What tests are recommended when agenesis of the corpus callosum is first detected during pregnancy?

When agenesis of the corpus callosum is suspected, further testing is often recommended. First, the agenesis needs to be confirmed and this may only be possible through a high-quality MRI scan. If the diagnosis was made before birth, an additional or repeat MRI may be recommended once the baby is born. This can help assess whether it is complete or partial agenesis and if any further brain abnormalities can be seen.

Parents often ask whether brains scans need to be repeated. A neuro-radiologist will be able to comment on whether your scan is of good quality and if another scan is warranted (e.g., the image is distorted because of movement or if the findings on the scan require follow up to monitor for changes).

Because a disorder of the corpus callosum may be associated with chromosomal or genetic abnormalities, genetic testing may be recommended. This can be through non-invasive prenatal testing (NIPT) where a blood sample is taken from the mother during pregnancy from which fetal DNA is isolated. More invasive procedures may also be recommended, such as amniocentesis or chorionic villus sampling (CVS) which uses a fine needle to collect either a small sample of amniotic fluid that surrounds the baby (amniocentesis) or a small sample of cells from the placenta (CVS). Blood tests can also be taken from the baby after birth.

Genetic testing, such as a *chromosomal microarray*, a *karyotype test* or *analysis of a panel of genes* is often used when there is a suspected genetic cause for some abnormality in development. More recently, methods such as whole exome sequencing are being used to examine the many different genes that instruct body development. The purpose of these tests is to try to determine whether genetic changes are likely to be responsible for the disruption in the development of the corpus callosum.

With the advancement of genetic testing in recent years, it has been estimated that around 30 to 45% of individuals with agenesis of the corpus callosum now have a known genetic cause for their brain abnormality. Although the genetic causes are wide-ranging in themselves, research in this area can lead to a better understanding of why the corpus callosum failed to develop properly and may help to predict the nature of future problems.

Further tests will help determine whether the disorder of the corpus callosum is an isolated condition or if it coexists with other brain or genetic abnormalities

What else might be seen on the brain scan?

Colpocephaly: enlargement of the occipital horns; this is the end portion of the lateral ventricles of the brain (i.e. the fluid filled cavities) which can expand and assume a distinctive 'tear-drop' shape. See next page for examples.

Probst bundles: the nerve fibres of the corpus callosum that were not able to cross between the two hemispheres, instead get rerouted and form neural tracts within each hemisphere; Probst bundles may still have a role in transferring information in the brain and could compensate for the absent corpus callosum.

Interhemispheric cyst: a pocket of fluid between the two brain hemispheres; these may vary in size.

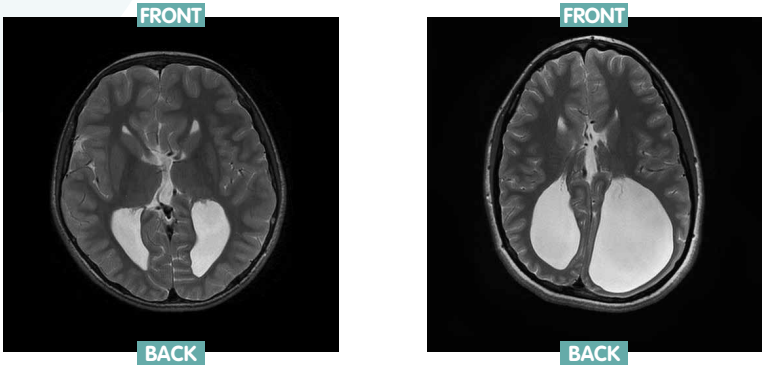
Heterotopia or heterotopic grey matter: common malformations of cortical development; describes cells that grow toward, but do not reach, their typical destination and are located in the wrong part of the brain; in grey matter heterotopia, clumps of grey matter may be seen within white matter.

Abnormal cortical gyral patterns: the folds or bumps (gyri) on the surface (cortex) of the brain form a different pattern to typically developing brains; the role of the folding is to create separate brain regions and increase the brain's surface area.

Posterior fossa anomalies: the posterior fossa is located at the base of the brain and contains the cerebellum, brainstem and 4th ventricle; the cerebellum is responsible for cognition (learning and understanding) and for balance and coordinated movements; the brainstem is responsible for controlling vital body functions, such as breathing.

Intra-cranial or pericallosal lipoma: fat-containing mass that can occur in the deep groove that separates the two hemispheres of the brain (inter-hemispheric fissure). These lipomas are thought to have formed very early in brain development, at the point the corpus callosum was not forming correctly. They are usually not harmful so do not need to be removed surgically.

Hydrocephalus or hydrocephaly: an abnormal build-up of cerebrospinal fluid (CSF) in some or all of the ventricles of the brain; the ventricles become enlarged and may place pressure on the tissues of the brain; it can be treated by a surgically implanted tube (shunt), which diverts fluid to another area of the body where it can be absorbed.



MRI images (taken through a horizontal plane) showing different examples of colpocephaly (enlarged lateral ventricles of the brain) which often co-occur with agenesis of the corpus callosum.

Will my child need another MRI scan when they are older?

Brain scans performed on infants can lack some detail because the brain undergoes a lot of development in the first few years of life. A repeat MRI scan when your child is older may provide more information. In some children another MRI scan is obtained because they develop new symptoms, such as seizures. It is a good idea to keep copies of all the brain scans that are performed because if something changes in the future, you will have a baseline for comparison.

Why does agenesis of the corpus callosum happen?

Agenesis of the corpus callosum is caused by a disruption in the migration of brain cells during early development of the unborn child. During the formation of the corpus callosum, something interrupts the movement of the nerve fibres that were destined to cross over to link the two brain hemispheres. In complete agenesis something interrupts this process very early so that no nerve fibres begin to form or do form but fail to cross. In partial agenesis nerve fibres begin to cross but are interrupted such that only part of the corpus callosum forms.

The formation of the corpus callosum is a complex process and a large number of interacting genes are involved in its development between the 7th and 20th week of pregnancy. As a consequence, there can be many different reasons behind why the formation becomes disrupted in some way. Some of these causes can be identified – but for many individuals, the reason for the disruption remains unknown.

Known causes of disruption in the normal development of the corpus callosum include:

- Genetic or chromosomal changes: a faulty gene may have prevented the neural circuits in the brain forming properly. Currently this is the most common known cause of callosal abnormality with up to 45% of individuals having a change in a specific gene or chromosome pattern. Some genetic disorders may be passed on from parent to child, but most develop as a sporadic genetic fault that is not inherited and occurs by chance.

- Viral infections: an infection or virus in the womb (e.g., rubella) may have interfered with the developing brain early in pregnancy; often such infections go unnoticed and the mother would not have been aware of them.

- Exposure to certain toxins or medications: exposure to certain drugs or excess alcohol can increase the risk of a child being born with a callosal disorder.

- Disruptions to normal brain development: such as the development of a cyst that may have blocked the growth of the corpus callosum.

Will it be possible to identify the cause?

All of the tests done by health professionals both before and after diagnosis of a disorder of the corpus callosum aim to find clues to the underlying cause of the problem. In many cases doctors may not be able to find the exact cause for the condition; however, over time new clues to a diagnosis may surface as new tests are developed. It can therefore be useful to stay in touch with the health professionals involved in your child's care in case any new developments are applicable to your family.

> "Agenesis of the corpus callosum can be understood as 'an accident of genetics.' We have some understanding now of some of the cells that are required for forming a bridge between the hemispheres to allow the corpus callosum axons to cross over, and that developmental process is controlled by a large range of different genes. If a person happens to have a mutation in one of those genes, then often agenesis of the corpus callosum occurs"
>
> **Professor Linda Richards, Queensland Brain Institute**[i]

Did I do anything during my pregnancy to cause it?

No. This is a common concern of parents and very understandable. Disorders of the corpus callosum are the result of changes in brain development very early in pregnancy, sometimes before the mother is aware she is pregnant. Avoidance of alcohol in any pregnancy is advised and there is some evidence that alcohol can be a contributor to the cause of some disorders of the corpus callosum (e.g., as a feature of fetal alcohol syndrome). However, in most cases it is probably fair to say that nothing could have been done to avoid the malformation.

If I have more children are they likely to have a disorder of the corpus callosum as well?

The chance of further children in a family having a disorder of the corpus callosum will depend on whether the affected child has an underlying genetic disorder or syndrome. Sometimes a known syndrome is suspected by the presence of other features, such as a cleft lip/palate or differences in how fingers have developed. However, there are many thousands of different genetic conditions, a proportion of which have agenesis of the corpus callosum as a feature, so each child needs to be assessed individually.

Some genetic abnormalities may have only occurred for the first time in an affected child, in which case the chance of it happening again in another child is lower. In others, agenesis of the corpus callosum is part of a condition due to a gene or chromosome change inherited through the family and the chance of it happening again may be higher.

Where a disorder of the corpus callosum is thought to have occurred as a result of an infection or exposure to medication, drugs or excess alcohol, the risks of it recurring is reduced if the same exposure does not occur in the next pregnancy.

A clinical geneticist will be able to look for signs of a syndrome and advise on whether any genetic testing is indicated and what this might find. Genetic testing has moved on very rapidly over recent years and there are a growing number of tests to look for changes in genes and chromosomes. This means that even if nothing is found now, or has been found previously, a cause may still be found in the future.

Can a disorder of the corpus callosum occur in more than one member of a family?

Syndromes that include agenesis of the corpus callosum as a feature, can be inherited through families or occur for the first time in an affected person. There is a possibility that other members of the family also have a disorder

of the corpus callosum. For the majority of families however we are currently unable to say for certain how the disorder of the corpus callosum has happened in an individual and how likely it is to happen again.

What other conditions and genetic syndromes are associated with agenesis of the corpus callosum?

If you search the internet for *agenesis of the corpus callosum*, you will find that it is associated with a high number of conditions, some of which can have a severe impact on development. There are actually over 200 genetic syndromes that can include agenesis of the corpus callosum (e.g., Dandy-Walker syndrome, Andermann syndrome), most of which are very rare. Other brain abnormalities can also impact on the formation of the corpus callosum; for example, Arnold-Chiari malformation, schizencephaly (clefts or deep divisions in brain tissue), holoprosencephaly (failure of the forebrain to divide into lobes), hydrocephaly and migrational anomalies.

Agenesis of the corpus callosum is also associated with several chromosomal anomalies, including trisomy 13 and 18. When the corpus callosum disorder is part of a broader genetic syndrome, specific medical complications may appear. These individuals may require medical intervention for seizures or other medical problems they have in addition to the callosal disorder. For example, girls may have a gender-specific condition called Aicardi syndrome, which causes severe intellectual disability, seizures, abnormalities in the vertebra of the spine and lesions on the retina of the eye.

Finally, disorders of the corpus callosum can also be associated with malformations in other parts of the body, such as midline facial defects, visual system malformations (e.g. optic nerve hypoplasia), hearing problems and heart defects. Not only are these important to identify and treat where necessary, they can also be important clues to the underlying cause and diagnosis.[ii]

What will my child be like in the future?

The impact of a disorder of the corpus callosum on development is very varied, even when the patterns of brain abnormalities look relatively similar between individuals. Some children may have severe intellectual and learning difficulties, while some appear to develop much like their peers.

The main feature that seems to determine outcome is the extent and severity of other malformations and neurological conditions, such as the presence of seizures or other changes in the brain structure, such as cysts or cerebellar abnormalities. When agenesis of the corpus callosum appears to be *isolated*, that is without accompanying neurological problems, the outcome can be more favourable. A recent survey of individuals diagnosed with isolated agenesis of the corpus callosum before they were born, found 75% of children had essentially normal development; the remaining children had differing levels of intellectual disability, with around 12% having severe learning problems. These findings have some limitations as the children were only assessed when they were young and only on a few measures. It has been reported that even when children have normal intelligence, a range of behavioural and social difficulties may develop over time. Although there is no "typical behaviour pattern" that fits all children with disorders of the corpus callosum, common symptoms have been described by parents and are listed in the following section.

> "It will be interesting to see how his development continues, I worry much less now than I used to. For the first 12 months I obsessed about "normal" and "abnormal" development and then I reached a point where I realised he would learn things when he was ready. I just want to enjoy time with him and his brothers so that's what I'm doing"
>
> **Mum of a 2-year-old with complete agenesis of the corpus callosum**

What problems may be seen in early childhood?

Newborns with a disorder of the corpus callosum may not show any problems straight away, especially if they have no other associated conditions. Common areas of concern that might become more apparent during infancy and early childhood include:

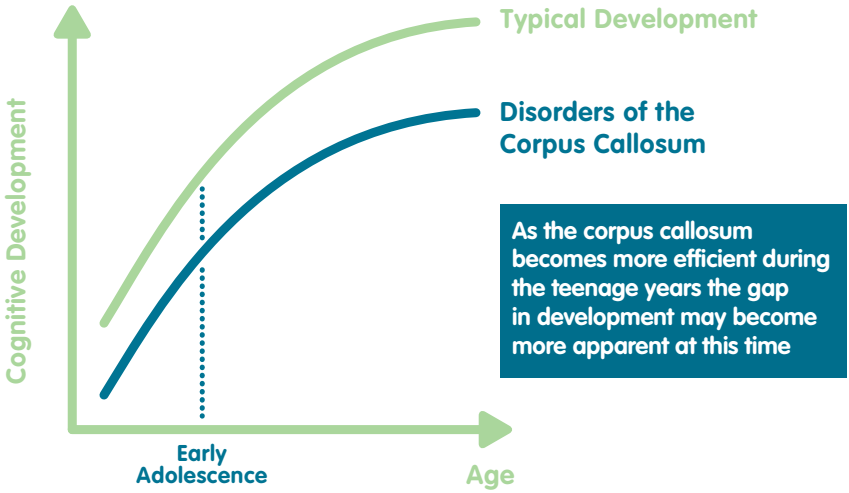
- Poor feeding and difficulty swallowing
- Delays in reaching developmental milestones, such as holding the head upright, sitting and standing up, walking and talking
- Problems with vision, such as judging depth and distance
- Problems with hearing
- Poor muscle tone and coordination
- Sleep problems
- Increased sensitivity to certain sensations, such as temperature, food textures and touch
- High tolerance to pain

> “Our son’s agenesis of the corpus callosum was suspected before birth, and then confirmed shortly after he was born. At the time, we were told that there was a wide range of outcomes, from having no problems at all, through to more serious learning difficulties. We were told that there were people who had this abnormality and you wouldn’t know unless you asked them to do something like draw a picture with one eye closed – this was not helpful! ”
>
> **Mum of a 7-year-old with partial agenesis of the corpus callosum**

What problems may be seen in late childhood and adolescence?

Although every child with a disorder of the corpus callosum is different, the problems that family, friends or teachers notice can change or become more apparent in later childhood and adolescence. Problems that seem to "emerge" around this time can include difficulty in planning and organising, solving complex problems, regulating emotions and thinking more abstractly. Social difficulties can also become apparent and they may seem socially immature for their age.

We know that throughout childhood and through the teenage years, the nerve fibres of the corpus callosum continue to grow and become more efficient. The insulating coat (myelin) of the fibres thicken, allowing for better flow of information between brain regions. Around this time children with a normally formed corpus callosum make progress in their cognitive development, particularly in abstract reasoning and problem solving, and their social skills mature. A child with a disorder of the corpus callosum can often keep up with their peers until this age, but may then begin to fall behind in schoolwork and social functioning. But rather than a loss of functioning, it seems to be the increased reliance on the corpus callosum during adolescence that drives the growing difference between them and their peers.



Common areas of concern that might become more evident during late childhood and adolescence include:

- Motor coordination difficulties, particularly on skills that require coordination of feet and hands, such as swimming and bicycle riding
- Difficulty with complex tasks that need abstract thought and problem-solving
- Slow processing speed
- Difficulties paying attention
- Poor understanding of non-literal language - such as recognising the difference between what someone says and what they really mean (e.g., the use of sarcasm, humour, irony)
- Difficulty identifying what someone is feeling from their tone of voice or facial expression
- Showing some degree of social awkwardness or social naivety, such as being overly friendly to strangers
- Difficulties in some academic skills, particularly in mathematics

> "It has opened my eyes having a daughter like her. I am from a very academic background and it used to be the be-all and end-all. My daughter probably won't be academic, but there's more to life than academic success. Now as a mum I just want her to be happy, this means so much more to me"
>
> **Mum of a 3-year-old with complete agenesis of the corpus callosum**

> "Things do tend to take longer, like learning to swim, learning to ride a bike but she now has the attitude that she knows she will get there eventually – and she will get there!"
>
> **Mum of a 15-year-old with partial agenesis of the corpus callosum**

Does it matter what part or how much of the corpus callosum remains?

There are often similar outcomes between individuals who have part of the corpus callosum remaining and those who have all of the structure missing. There is some evidence that partial agenesis may occur slightly more often with complex forms of agenesis of the corpus callosum, that is, when there are additional, complex alterations of the brain. Individuals with partial agenesis may therefore have a greater range of difficulties than complete agenesis. But overall, the research suggests that outcome for those with complete agenesis is the same as those who have part of the corpus callosum remaining.

This research is ongoing as scientists think the mechanisms behind the disruption in development must differ between the two conditions - for example, in the timing of the disruption. Research is also continuing into whether the amount of corpus callosum that remains relates to the variation in outcome and to what extent other factors, such as the presence of existing commissures and other brain and genetic factors, can explain the variability.

> “School is so incredibly hard for her. Word retrieval is often a problem and her processing speed is very slow. This makes communication difficult. She needs a little extra time to think and organise her thoughts. She is very literal in her words and thoughts - things are black or white. Nonverbal cues and body language are things often lost on her ”
>
> **Mum of a 16-year-old with complete agenesis of the corpus callosum**

Will it get any better or worse?

After the critical period of brain development during pregnancy no new fibres form in the corpus callosum and the appearance you see on a brain scan will not change. It will not progress or get any worse. However other changes in the brain can occur and may cause new symptoms. For example, occasionally interhemispheric cysts can enlarge and cause symptoms such as headaches

or nausea because of the increased pressure on the brain. Such cysts may need an operation to drain the fluid. If new symptoms occur then your doctor may request additional scans or tests to identify any possible changes.

Even though the appearance of the corpus callosum does not change, as the rest of the brain continues to grow and develop across the lifespan, the effects of a malformed corpus callosum may become more obvious. In this sense, the symptoms of agenesis of the corpus callosum may "get worse" with age. However, often individuals learn coping skills well into adulthood, so they may also get somewhat "better" over time.

> "The main problem was her frustration with articulating her thoughts and wants. I could almost see her brain calculating. This delay from brain to words frustrated her. It often resulted in temper explosions that school could not handle. Now, my daughter has a two-year college degree and works at a day-care. Never temper problems at work. Occasional upsets at home, but who doesn't have them?"
>
> **Mum of a 28-year-old daughter, diagnosed with complete agenesis of the corpus callosum soon after birth**

Why are social skills such a common concern in disorders of the corpus callosum?

The skills needed to get along with other people are incredibly complex. Even being able to maintain a conversation requires multiple skills such as the ability to listen and respond appropriately, read body language and adapt the conversation accordingly. As well as following the conversation, there may be a need to show empathy and appreciate the point of view of another person. Moreover, conversations are often fast-paced and several areas of the brain have to work together efficiently and effectively in order to keep up. It is not surprising that social skills are often compromised when the wiring of the brain has not formed typically or is damaged in some way.

OUTCOME

Parents often describe their child with a disorder of the corpus callosum as very sociable, and form affectionate ties within the family. However, particular areas of difficulty can arise in social situations. Although they enjoy being around other people, they may lack awareness of social boundaries and can come across as much younger than their years. Children may have difficulty forming friendships with peers, preferring to spend time with younger children or with adults. Problems can become more evident in the teenage years as social interactions become more challenging and complex. Because of the difficulties with social interaction and communication, autism is sometimes considered as a diagnosis.

> “He really likes other children; he likes being with his older brother and sister but more likes watching their games and get ideas from what they are doing. He is not very good at initiating things with children his own age. He feels really safe with adults; he will go over and talk with adults about anything he is interested in. I guess they will come back and have a good conversation with him and he’s probably not so sure what to expect from children his own age ”
>
> **Mum of a 7-year-old with complete agenesis of the corpus callosum**

> “She has difficulty keeping up with her peers, from a social perspective, mixing with them, and understanding what is going on. She understands the nuances, irony, and jokes - sometimes she gets things before I do! But I think it is to do with the processing and the quick-witted humour and chat - I think she gets a little left behind ”
>
> **Mum of a 15-year-old with partial agenesis of the corpus callosum**

> “Her struggle with social situations is the hardest part for me, as her mum. I love that she is not as socially and emotionally mature as her peers, but it is painful to see her struggle to make and keep true friends. She is a beautiful and caring young lady, but often her peers do not give her a chance to show just how wonderful she is ”
>
> **Mum of a 16-year-old with complete agenesis of the corpus callosum**

Can my child get a diagnosis of both a disorder of the corpus callosum and autism?

Autism is defined by a constellation of problems in social communication, social interaction, and restricted and repetitive patterns of behaviour. Autism is recognised to have a biological basis although, despite much research, the exact genetic, neurological or other biological causes remain unknown. It is likely to stem from multiple factors, including a large genetic component and also environmental factors that impact brain development. There is therefore no medical test for autism and a diagnosis can only be made by behavioural signs.

In contrast, a disorder of the corpus callosum is a physical diagnosis, based on a clear anatomical difference in the brain. Behaviour can vary widely in those with the same brain abnormality. However, some behaviours described in agenesis of the corpus callosum show many similarities to those seen in autism, particularly in impaired social interaction and communication. A diagnosis of autism, or Autism Spectrum Disorder (ASD), may be appropriate for a child with a disorder of the corpus callosum who presents with marked social and communication difficulties that significantly impact their functioning. In fact, recent studies have confirmed that up to one-third of adults with isolated agenesis of the corpus callosum meet the diagnostic criteria for autism. This was regardless of whether or not they showed symptoms of autism early in life.

It is surprising that not more individuals with disorders of the corpus callosum receive a formal diagnosis of autism, given the behavioural similarities. This may reflect diagnostic overshadowing where additional problems can be overlooked. The clinician may "stop" at the primary diagnosis of agenesis of the corpus callosum, despite the child meeting diagnostic criteria for autism. Some common symptoms of autism may not be seen in agenesis of the corpus callosum, for example, the repetitive and restricted interests and other non-social behaviours. Social difficulties may only be noticeable at later ages when social demands are higher; this may also prevent a formal diagnosis of autism. For some children a diagnosis of autism can be helpful as many teachers will be familiar with the learning styles of autistic children, but few will have any knowledge of disorders of the corpus callosum.

The question still remains as to whether the "autism" is the same in both conditions. For example, the symptoms may appear similar, but the underlying reasons for the difficulties could differ. This question is being addressed in ongoing research. It may be that disruptions in the development of the corpus callosum is one of many causes of autism. Indeed, one theory maintains that the wiring in the brains of autistic people is abnormal, particularly with the long-range connections between different brain areas. The corpus callosum has also been found to be thinner in some people with autism. However not all autistic individuals have a disorder of the corpus callosum, and vice versa, not all individuals with a disorder of the corpus callosum will have autism.

What about other clinical diagnoses?

In addition to autism, a number of children with disorders of the corpus callosum will show behaviours that might qualify for other diagnoses. Some children who have problems with motor coordination may be diagnosed with dyspraxia or developmental coordination disorder (DCD). Children with specific difficulties in learning to read and write may receive a literacy disorder diagnosis, such as dyslexia. Children with high levels of hyperactivity and inattention may reach criteria for a diagnosis of attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD). Anxiety, obsessive and compulsive behaviours may also be seen at a high level and may need to be recognised as an additional condition.

Similar to autism, all of these conditions are diagnosed through behavioural observations, for which the brain causes are unclear. It is not currently known how these additional clinical diagnoses may relate to the brain differences seen in disorders of the corpus callosum; that is, if they are a further expression of the brain difference or simply coincide. Researchers are continuing to examine how these additional difficulties are linked to agenesis of the corpus callosum.

Whether the reasons behind the additional problems are directly related to malformations in the corpus callosum or not, for an individual child it is important to have any additional problems recognised and appropriate remedial interventions in place. Social skills training programmes designed for children with autism, for example, may still be appropriate and adapted

for children with disorders of the corpus callosum. Children will also benefit in school from accommodations (e.g. in exams) for dyslexia, ADHD, etc. if these are relevant.

Can disorders of the corpus callosum ever occur without any problems?

Some people may be missing their corpus callosum without ever being aware of it. There are many reports of people discovering they do not have a corpus callosum by chance because they had an MRI scan following an accident or when they participated in research. Could the condition therefore ever be asymptomatic - that is, without any obvious problems?

This question often arises, especially when studies report that for a proportion of people with isolated agenesis of the corpus callosum, outcome can be very favourable – they perform well on measures of intelligence and are doing well at school. This may not provide a full picture of outcome however and subtle problems may occur.

Researchers currently agree that disruption during the formation of the brain must have consequences, even if they appear mild. Some developmental delays and deficits associated with disorders of the corpus callosum are often difficult to notice, and the outcomes vary widely, which may be the reason why it can go undiagnosed for years.

> “Some individuals do so well that some people think that callosal agenesis has no impact on functioning. But even those who are most successful usually have subtle language and social impairments”
>
> **Dr Lynn Paul, Senior Research Scientist,**
> **Caltech Emotion and Social Cognition Laboratory in Pasadena, California**[iii]

OUTCOME

Some people who discover their brain difference later in life have described always knowing that "something was not quite right". Learning of the condition seemed to help put things in place and provided some explanation to why they felt like they had struggled with certain aspects of their lives.

> "I had an MRI scan and there it wasn't (my corpus callosum). This was all so surprising, even the specialist didn't pick it up at first. His first comment to me was that I should hang up my chainsaw! The initial shock of the news was profound, but then I realised it answered more questions than it asked. It explained my lack of academic success. The difficulty I'd always had taking in new information. The feeling that something wasn't wrong but it wasn't right either. The lack of an obvious direction to pursue for work. The ability to concentrate on only one thing at once, so no multi-tasking or juggling a busy schedule"
>
> **James, learned at age 38 he had complete agenesis of the corpus callosum**

> "I was diagnosed in my 30s. I was told my entire life I was born with a brain injury. Never thought it to be agenesis of the corpus callosum until all the symptoms matched what I was feeling. You don't "get better" you learn to live with it. It's not a disease, it's a rare genetic birth defect. I struggle big time with my memory and verbal directions. I was told I would never hold down a job. But I work in a school for kids with Autism"
>
> **Nadine, diagnosed with complete agenesis of the corpus callosum**

What treatments are available for disorders of the corpus callosum?

Currently, there are no direct treatments to restore the corpus callosum to normal. As problems with the development of the corpus callosum happen very early in pregnancy, it is not possible to change this later. The main course of treatment is to manage any symptoms that may arise over time.

It is good to monitor your child's progress so support can be given as soon as a problem emerges. Early diagnosis and early interventions are currently the best treatments to improve social and developmental outcomes – although it is never too late to help a young person through educational and emotional support. Therapies that target inter-hemispheric coordination (e.g., tasks that need both hands working together) may be beneficial, particularly at a young age in order to take advantage of the plasticity of the developing brain.

Like many children and adults with specific physical or learning difficulties, those with a disorder of the corpus callosum are likely to benefit from a variety of interventions and specialist help at home and at school. If you have any concerns with the development of your child, you should ask your GP or family doctor to make a referral to see a specialist.

Can stem cell therapy work for the corpus callosum?

At the current time, scientists believe that stem cell treatment are not likely to be effective for treating corpus callosum disorders. Stem cell replacement is effective in conditions where cells were originally intact and therefore can be "replaced". In complete or partial agenesis of the corpus callosum, these cells were absent from the start and cannot simply be replaced. The brain has organised itself without the connecting fibres of the corpus callosum and therefore would not be able to accommodate these connections, even if they could be introduced.

What professional support is available?

Once a person receives a diagnosis, the help available will depend on their age and level of development and learning. However, there are many therapies and supports available that may help individuals with disorders of the corpus callosum lead more successful lives.

For Young Children…

Changes in the corpus callosum are often diagnosed during early childhood because of concerns about development, speech, or other problems such as seizures. It is likely that your child will have had a number of investigations as well as a brain scan, such as blood and urine samples. This is often a time where there are a number of appointments with different professionals, including an Ophthalmologist (eye specialist), Endocrinologist (hormone specialist), Neurologist and Clinical Geneticist for their opinions. This can be a frustrating time as it can feel that no one knows what is wrong with your child.

The majority of children will have a Paediatrician (often a Community Paediatrician) who will be able to assess their development, coordinate their care and put you in touch with other professionals and therapists, such as Social Workers, Occupational Therapists, Physiotherapists and Speech and Language Therapists. The involvement of health professionals will depend on the level of difficulties your child has. Numerous hospital appointments can be difficult for families to organise and keep track of. This may change as your child grows and you may find it useful to keep a record of the people involved in their care.

Do not be afraid to ask questions and find out as much as you can about your child's individual problems. The answers may be helpful in making decisions about your child's current and future needs. Every child is an individual and although they are likely to share some of the features of agenesis of the corpus callosum with other affected children, they will still have their own unique personality and developmental path. It is not possible to predict exactly what will happen to a child as they grow up or what level of care they will require, although the health professionals involved in your child's care will be able to give you more advice and support about this issue. For many parents it is a matter of 'wait and see'.

For School-Aged Children…

Children who have a diagnosis before they start school will already be involved with a Paediatrician and possibly a Child Development Team. Your Paediatrician will know whether your child is likely to need any extra support when they start school and, with your permission, will inform the Education Department so they can gather information from everyone involved with your child and make sure they have the right support from the very beginning of their school life.

Some children will have already started at school by the time the diagnosis is made and you may or may not be aware of difficulties they are experiencing. You may find it useful to arrange to talk to your child's teachers to explain the brain differences that have been found and discuss your child's progress in more detail. It is unlikely that any of your child's teachers will have heard of callosal abnormalities or had experience of dealing with children with the condition. Sharing this booklet with anyone working with your child may be helpful.

Your child may require extra help at school and it is best to talk to your child's teachers (particularly teachers who have had additional training with children who need support) about what help they may need and how this may be provided. Your child's school may be able to assess this and provide the support, or they may feel your child needs a deeper assessment of their strengths and weaknesses by an Educational Psychologist.

As children get older, some of the social and communication problems associated with disorders of the corpus callosum can become more obvious. It may be helpful to talk to your child's teacher about this. Although we cannot change the brain malformation, many of the challenges faced by an individual with a disorder of the corpus callosum are amenable to appropriate help and intervention. Speech and Language Therapists and Psychologists may be able to help your child in these areas. It is important that, where possible, you talk to your child openly about issues as they come up and develop strategies together to deal with them.

For Adults…

Occasionally an abnormality in the corpus callosum is found incidentally on a scan done for another reason, such as a head injury. In others, development of other problems such as seizures may prompt further investigations like a brain scan. For a person diagnosed in late adolescence or adulthood the diagnosis can come as a considerable shock as they are often unaware that there has been any difference in the way their brain has formed. For some individuals it can feel like an explanation for difficulties they have experienced throughout their life.

It may be useful to talk to a Neurologist about the changes on a scan in more detail. If this has been an incidental finding and you are otherwise well, there are often no regular medical checks that need to be arranged. As the findings on the brain scan will not change it is unlikely that this will affect your health in new or unexpected ways. You may find it useful to talk to a Clinical Geneticist if there have been any other unexplained developmental problems or there are concerns about other members of your family, or the possibility of future children inheriting your condition.

Discovering that you are missing an important brain structure can be very scary and confusing. Even within the medical community, there is not always awareness of disorders of the corpus callosum and what this means. It is good to be aware of the range of outcomes that are possible with this brain difference and how well the brain can adapt when the corpus callosum fails to develop properly.

> “It is important to manage your own energy levels and recognise when you are getting overwhelmed and take appropriate action. Ask for help when you need to and let other people know when you need more time to process things”
>
> **Advice for adults with disorders of the corpus callosum**
> **Dr Lynn Paul, Senior Research Scientist, Caltech Emotion and Social Cognition Laboratory in Pasadena, California**

How can I connect with other families and individuals affected by disorders of the corpus callosum?

There are now a number of groups established around the world that can provide support to families and individuals affected by disorders of the corpus callosum. They often arrange annual meetings and family get-togethers and can be an important resource. Meeting other families going through similar experiences and having the opportunity to share information and advice can be hugely beneficial for all.

Corpal
DCC & Aicardi Syndrome UK

www.corpal.org.uk
info@corpal.org.uk

National Organization for Disorders of the Corpus Callosum

www.nodcc.org
info@nodcc.org

assacci
Associazione Anomalie Corpo Calloso Italia

www.assacci.it
agenesiadelcorpocalloso@gmail.com

ausDoCC
australian disorders of the corpus callosum

www.ausdocc.org.au
info@ausdocc.org.au

Association RACCORD

@AssociationRACCORD

ABrDCC
ASSOCIAÇÃO BRASILEIRA PARA DESORDENS DO CORPO CALOSO

@dccbr

"I discovered Corpal shortly after my child was born and have found it a great source of reassurance and support. It was lovely going to the North of England meeting when he was very small and meeting other children with the condition.

The Facebook page is a great place for talking to other parents who get how it feels. I sometimes find myself talking to women who have had a diagnosis in pregnancy and I just hope that speaking to someone who knows what a scary time it is, helps them a little"

Mum of a 2-year-old with complete agenesis of the corpus callosum

"It is good to make contact with other people as you don't come across this in day-to-day life and most people have never heard of it. Hopefully with time and with more research, it won't be considered so rare"

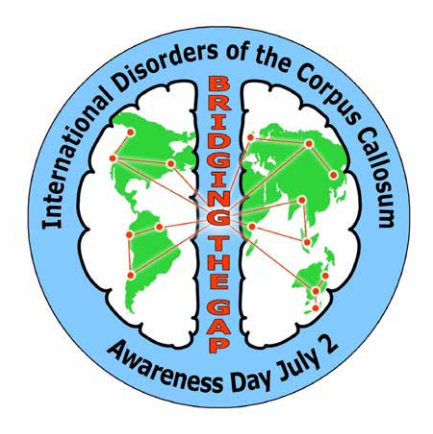
Mum of a 3-year-old with complete agenesis of the corpus callosum

"We didn't know much about the brain and how it works, so when someone tells you that the key bit down the middle is missing – that's really big. You have no understanding of what it actually means and we were given the worst-case scenario. Seven months later, it is nowhere near as bad as it felt like at that moment when you are told. It is only coming to this family meeting that you realise it may not necessarily be the worst-case scenario"

Dad of a 6-month-old with complete agenesis of the corpus callosum

> “Connecting with other people is the biggest thing, because that is when you get to talk to people and you have some understanding of how they are feeling. You could be facing really serious challenges, you might not be, but at least you can tell them that you’ve been through it as well ”
>
> **Mum of a 6-month-old with agenesis of the corpus callosum**

> “You are told it is a rare condition and that there is not a lot of information – but being able to share with other families on Facebook has been so helpful for us, even though I have never met these people. It is so diverse but at least you are sharing and you don’t feel like you are on your own ”
>
> **Mum of a 12-month-old with partial agenesis of the corpus callosum**



July 2nd marks the midway point of the year – the point when the two parts of the year are connected — just like the corpus callosum bridges the two halves of the brain. It is at this special moment in the year that we celebrate **International Disorders of the Corpus Callosum Awareness Day.**

DCC Awareness Day was established in 2015 by the NODCC, AusDoCC and Corpal

What research is being done to increase our understanding of disorders of the corpus callosum?

Of all the objects in the universe, the human brain is often said to be the most complex and therefore the most difficult to study and understand. Recent advances in the technology of brain-scanning methods have allowed scientists to start to unravel some of the "mysteries" of how our brains work. Of particular interest is how brain regions communicate and connect with each other and the role of the corpus callosum is central to this.

Understanding what happens in the brain when connections are missing or altered can provide insight into both typical and atypical brain development. Although the effects of a disorder of the corpus callosum cannot be reversed or cured, scientists worldwide are working towards understanding the possible causes and the nature of the consequences on brain development, cognition and behaviour. Ultimately, the goal of this research is to develop effective treatment and strategy options for improving the lives of people with disorders of the corpus callosum.

Research aims

To identify the underlying genetic cause

Can we better understand the mechanisms behind why disorders of the corpus callosum occur?

Scientists are working towards identifying the genes that are involved in the development of the corpus callosum and what mechanisms may cause the disruption in its formation. Finding an underlying genetic cause would provide a way to classify the condition or syndrome and work towards being able to predict how a child will function in the future.

To understand brain plasticity

How does the brain reorganise following a disruption very early on in development?

Researchers are looking at what happens in the brain when the corpus callosum does not form correctly. One question is how the two sides of the brain still manage to communicate with each other and transfer information despite the absence of the corpus callosum. Are there alternative pathways that still connect brain regions that may compensate for the lack of the corpus callosum?

To predict outcome

Can we determine what someone will be like in the future based on information in their brain scan?

Researchers are trying to understand whether different patterns of brain wiring may relate to an individual's cognitive profile – that is, their own pattern of strengths and weaknesses. Some connections may be essential, while others could be compensated for and not as essential as previously thought. Understanding the role of different patterns of brain wiring may help explain why people with disorders of the corpus callosum have widely different symptoms and outcomes.

To understand the long-term impacts on cognition and behaviour

How do disorders of the corpus callosum affect the ability to function in everyday life?

By following up children and adults over time, researchers will be able to study the impact the condition has on various aspects of life such as schooling, making friends, future employment and quality of life. Once this is understood, researchers and clinicians will be in a better position to tell families the possible challenges their child may face in the future and suggest ways in which they could overcome these challenges.

It is important to also follow children from birth to study the natural progression of the condition, rather than always asking parents to remember back to early milestones and behaviour. There is a risk of only studying children and adults where developmental concerns have been reported which could lead to biased findings. Ideally, population-based studies, where all babies with a disorder of the corpus callosum detected before or after birth, are followed over time will provide a more accurate and unbiased group to study. A longitudinal study which is tracking the development of babies and infants with disorders of the corpus callosum has recently begun in the United States and will be important in understanding how the disorder impacts individuals at different stages of their life.

For more information on this study, and other ongoing research into disorders of the corpus callosum, see the International Research Consortium for the Corpus Callosum and Cerebral Connectivity – IRC5 website: www.irc5.org

IRC5

International Research Consortium for the Corpus Callosum and Cerebral Connectivity

Agenesis of the corpus callosum (often shortened to ACC or AgCC): a rare birth defect (congenital disorder) in which there is a complete or partial absence of the corpus callosum. In complete agenesis of the corpus callosum, no fibres have managed to cross between the two sides of the brain. In partial agenesis of the corpus callosum, part of the corpus callosum has formed.

Aicardi syndrome: a rare gender-specific condition, in which girls have agenesis of the corpus callosum, retinal abnormalities (called chorioretinal lacunae), and seizures in the form of infantile spasms. Aicardi syndrome does not yet have an identified genetic cause although a change is thought to occur in a gene on the X chromosome. Studies of many families with Aicardi syndrome indicate that the recurrence risk is very low.

Andermann syndrome: a very rare genetic disorder (found almost exclusively in a part of Quebec) that damages the nerves used to control muscles; it is often associated with agenesis of the corpus callosum and learning disabilities.

Anterior: nearer the front, especially in the front of the body or brain.

Arnold-Chiari II malformations: structural defects in the base of the skull and the cerebellum, the part of the brain that controls balance; individuals can have agenesis of the corpus callosum, hydrocephalus, and incomplete closure of the spine (spina bifida).

Axon: also called nerve fibre; a long slender projection of a nerve cell that conducts electrical impulses away from the neuron's cell body. An enclosed bundle of axons makes a nerve, and becomes the primary communication lines of the nervous system.

Cavum septum pellucidum (CSP): is a split-like space or cavity which is present in the unborn child but usually fuses during infancy.

Cerebellum: part of the brain at the back and base of the skull that coordinates movement and sensation. It is also thought to be involved in cognition and learning.

Cerebral hemispheres: the main part of the brain that is divided into two halves or hemispheres.

Colpocephaly: enlargement of the lateral ventricles (cavities or chambers), particularly at the back of the brain. They are often described as 'tear-drop' shaped. This is a common secondary finding in abnormal formation of the corpus callosum.

Computed tomography (CT) or Computerised axial tomography (CAT scan): a well-established imaging technique using multiple X-rays.

GLOSSARY

Commissure: a connecting band of nerve tissue in the brain or spinal cord.

Corpus callosum: Latin for "tough body," the corpus callosum is the main connector that allows for direct communication between the left and right halves (hemispheres). It is the largest and most easily visible connection between the two hemispheres.

Dandy-Walker syndrome: a birth defect in which the cerebellum is malformed, the fourth ventricle is enlarged, the cerebellar vermis and corpus callosum is absent; there may also be a cyst at the base of the skull, and malformations of the heart, face, limbs, fingers and toes.

Disorders of the corpus callosum (DCC): the term used to describe any abnormality in the development of the corpus callosum. This includes when the corpus callosum does not develop (agenesis) or develops abnormally (dysgenesis).

Dysgenesis of the corpus callosum: abnormal development of the corpus callosum. This term covers any abnormality in the appearance of the corpus callosum.

Epilepsy: tendency to have recurrent seizures.

Grey matter: the part of the brain containing nerve cell bodies. Much of this can be seen on images as a layer over the surface of the brain.

Hemisphere: one of the two halves of the brain.

Holoprosencephaly: an abnormality of brain development in which the frontal areas of the brain do not properly divide into the left and right hemispheres and instead remains as one lobe; it may also be characterised by unusual facial features.

Hyperplasia of the corpus callosum: thickening of the corpus callosum, which may result from reduced axonal pruning after birth.

Hypogenesis of the corpus callosum: partial formation of the corpus callosum; also called partial agenesis. The corpus callosum develops in a 'front-to-back' direction - therefore we usually see the front portion of the corpus callosum present with the back missing. This can range from just a tiny area to the presence of most of the corpus callosum.

Hypoplasia of the corpus callosum: underdevelopment of the corpus callosum. Here the corpus callosum generally looks thin but with all of the parts present from front to back. Often all of the white matter of the brain looks underdeveloped as well.

Hypothalamus: a part of the brain with important roles many bodily functions including temperature, hormone function, appetite and sleep among others.

Interhemispheric cyst: a cyst is a fluid-filled space within the body; an interhemispheric cyst may occur between the two cerebral hemispheres either with or without an abnormality of the corpus callosum.

Interhemispheric fissure: also known as the medial longitudinal fissure; the deep groove within the midline separating both cerebral hemispheres.

Isolated agenesis of the corpus callosum: this diagnosis is made if no additional brain abnormalities are seen on brain imaging. By contrast, complex or 'syndromic' agenesis of the corpus callosum is used when there are additional, complex alterations of brain (or sometimes whole body) structures.

Lateral ventricles: hollow areas of the brain that are filled with fluid produced from tissue (choroid) within them, located in the middle of each hemisphere.

Malformation: a problem that occurs because of abnormal development of part of the body, for example a cleft lip or a callosal abnormality.

Malformation syndrome: sometimes just called a syndrome; a pattern of features, often with a unifying underlying cause, that arises from several different errors during a baby's development, for example Aicardi syndrome.

Magnetic resonance imaging (MRI): an imaging technique that uses magnetic signals, rather than X-rays to create image "slices" of the human body.

Myelin: the insulating coat that covers axons and facilitates transmission of information.

Nerve fibre: also called axon; a long slender projection of a nerve cell that conducts electrical impulses away from the neuron's cell body. An enclosed bundle of axons makes a nerve, and becomes the primary communication lines of the nervous system.

Neural plasticity: also known as brain plasticity, or neuroplasticity; refers to the ability of neurons to change in form and function in response to alterations in their environment. This can occur throughout an individual's life, although the younger developing brain can show a higher degree of plasticity and reorganisation than the adult brain.

Neuronal migration disorder: an umbrella term given to several conditions (including lissencephaly, agenesis of the corpus callosum and microgyria), which are suggested to share the same underlying cause, where neural circuits do not form properly during early brain development resulting in areas of the brain becoming abnormal or absent.

Pituitary gland: a hormone producing gland at the base of the brain which controls the production of other hormones throughout the body. It is directly connected to the hypothalamus.

Posterior: located behind, or towards the back of an object.

Probst bundles: the nerve fibres, which would have made up the corpus callosum, become rerouted and form neural tracts within each hemisphere.

Seizure: a sudden disruption of the brain's normal electrical activity accompanied by an altered conscious level and/or other neurological and behavioural manifestations. When someone has epilepsy, it means they tend to have epileptic seizures. Anyone can have a one-off seizure, but this doesn't always mean they have epilepsy. Epilepsy is usually only diagnosed if a doctor thinks there is a high chance that the person could have more seizures.

Schizencephaly: a rare birth defect characterised by abnormal clefts or deep divisions in the brain tissue.

Ultrasound: an imaging technique using high frequency sound waves. It is most commonly used to look at structures in the abdomen and during pregnancy. It can also be used to look at the brain in a newborn baby through the 'soft spot' (fontanelle) on the skull.

White matter: the part of the brain that contains nerve fibres covered (or which will be covered) in myelin. Myelin gives the white matter its colour.

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