

# Isolated corpus callosum agenesis

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## Abstract

*Corpus callosum agenesis (CCA) is the most common brain malformation with an incidence of 0.05 to 0.7%. It is characterized by the absence of the principal interhemispheric commissure, the corpus callosum. It can occur either as an isolated malformation (isolated CCA) (49% of cases), or in association with another malformation syndrome, including malformation of the forebrain, with viral infection, toxic or metabolic disease, chromosomal abnormalities. Clinical features include mental retardation (80%) and/or easily controlled epilepsy (50%) and/or behavioral disorders. However, clinical findings vary widely, ranging from asymptomatic with normal intellectual capacities to severe mental retardation. Isolated CCA appears to be related with a better prognosis than associated CCA with up to 80% of normal outcome. Radiological and genetic markers that would enable distinguishing between future asymptomatic and symptomatic disease are not yet available, making genetic counselling difficult when the condition is prenatally diagnosed. Diagnosis is based on cerebral imaging with transfontanel sonography (TFS), magnetic resonance imaging (MRI), computed tomography (CT). Prenatal diagnosis is now routinely made by ultrasonography (20th week) and MRI (30th week). Treatment is symptomatic and consists of physiotherapy, speech therapy, antiepileptic drugs and psychotherapy. To further understand the natural history of the malformation and to determine its outcome, data should be collected— using standardized evaluation tests and sufficient follow-up – in prospective studies on children with apparently isolated, prenatally detected CCA.*

## Disease name and synonyms

- Corpus callosum agenesis (CCA);
- Apparently isolated CCA;
- Corpus callosum dysgenesis;
- Partial or complete CCA.

the corpus callosum. This cerebral malformation is usually diagnosed in children undergoing examination for epilepsy or cognitive impairment, or less often, for behavioral problems.

## Diagnostic criteria/definition

Isolated CCA is characterized by the absence of the principal interhemispheric commissure,

## Differential diagnosis

Excluded diseases are CCA associated with:

- a known malformation syndrome: Aicardi, orofacioidigital, Anderman (CCA with neuropathy), Shapiro (spontaneous periodic hyperthermia), XLAG ...;
- chromosomal abnormalities;
- a metabolic disease (pyruvate dehydrogenase (PDH) deficiency, hyperglycinemia without ketosis, glutaric aciduria, ....);
- viral embryopathy;
- intoxication (drugs, alcohol) or medication (valproate ...);
- forebrain malformation (holoprosencephaly, septo-optic dysplasia);
- any brain or somatic malformation (lissencephaly, posterior fossa malformations, such as Dandy-Walker cysts, interhemispheric cysts).

These 'associated' agenesis are beyond the scope of our framework and share usually a poor prognosis in terms of psychomotor development; the severity of clinical features depends on the underlying pathology (*ie* severe epilepsy if lissencephaly).

Positive CCA diagnosis is easy to establish with MRI, but it is more difficult to ascertain whether or not the CCA is isolated. Clinical, biological, genetic and radiological evaluations are necessary to identify any etiology or eliminate any underlying disease.

### **Etiology**

The mechanisms leading to CAA are still unelucidated, however an anomaly of the commissural plaque, which is either a defective migration of the callosum axons or an abnormality of the callosum neurons, has been suggested.

Isolated CCA can be sporadic, autosomal recessive or dominant or X-linked. Although several chromosomes seem to be involved in the development and maintenance of the corpus callosum (1, 8, 13, 15, 18, 21, X ...), no gene has yet been identified for isolated CCA.

### **Clinical description**

Cognitive dysfunction includes learning difficulties, intellectual impairment, evaluated by IQ testing, and varies from mild (2/3 of the cases) to moderate and severe (1/3 of the cases). CCA is generally discovered when the child starts school.

Epilepsy consists of either partial or generalized seizures, or focal seizures with secondary generalization; this epilepsy is usually easily controlled and occurs in up to 50% of the patients with CCA; there is no data available concerning isolated CCA alone.

Behavioral or psychiatric disorders include emotional disturbances, attention deficit with hyperactivity disorder, and autistic features

have been associated with CCA. Facial dysmorphism can occur following the ventricular dilation accompanying the malformation: hypertelorism, protruding frontal bossing and/or macrocranium.

Despite these clinical findings, some children and adults with CCA are totally asymptomatic (Blum *et al.*, 1990; Pilu *et al.*, 1993; Vergani *et al.*, 1994) and there is no correlation with partial or total agenesis, sex, family history or obstetric complications. A prospective study (8 years follow up) was carried out on a population of 21 children prenatally diagnosed as having apparently isolated CCA. Neuropsychological evaluation was performed each year and results at the ages of 2, 4, and 6 years were compared. First results show that nearly 80 % of children are associated with a normal IQ (Moutard *et al.*, 2003). However with age, IQ tends to shift to the lower range (in 22% of children at 4 years and 29% at 6 years). Slowness, instability, attention and speech disorder appear at scholar age and cause learning difficulties. Some children need individual rehabilitation or orientation, even if IQ remains within the normal range. There is no epilepsy in that population but febrile seizures are more frequent than in normal population.

### **Diagnostic methods**

Clinical diagnosis needs to be confirmed by neuroradiological assessment with MRI. Patients with CCA may be asymptomatic and the malformation may be only discovered by brain MRI, for example in case of trauma. Cerebral imaging, transfontanel sonography (TFS) in the newborn, magnetic resonance imaging (MRI) in older patients, reveal a dilation of the occipital horns (colpocephaly) and an abnormal separation of the frontal horns that are parallel; the corpus callosum is not seen and the cortical gyri have a characteristic radiating disposition.

Karyotyping and the search for other associated somatic or brain abnormalities are required, as are blood samples to screen for metabolic diseases.

### **Prevalence**

CCA is the most common cerebral malformation (Jeret *et al.*, 1987). Classical data indicate that 0.05-0.7% of the general population and 2.3% of children with developmental disabilities are affected. The prevalence of asymptomatic CCA is unknown, but based on autopsy series or CT studies, it can be estimated to be 0.5/10,000 or 0.13-0.7%, respectively (Blum *et al.*, 1990; Gupta *et al.*, 1995).

### Genetic counselling

Parental counselling remains difficult in the absence of radiological and genetic markers that would enable distinguishing between future asymptomatic and symptomatic (20-30%) disease.

### Prenatal diagnosis

Prenatal diagnosis of this malformation is now routinely made by ultrasonography (20th week) and MRI (30th week).

### Management / treatment

Treatment is symptomatic: physiotherapy, speech therapy, antiepileptic drugs for epileptic seizures and psychotherapy.

### Unresolved questions

When isolated CCA is detected prenatally, sonographic or MRI findings, sex, or partial/complete CCA do not allow to predict the disease outcome. Larger series and longer follow-up in multicenter studies are needed to further understand the disease evolution and to identify the genes responsible for the development and maintenance of the corpus callosum.

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