Agenesis of the corpus callosum: female monozygotic triplets

Case report

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A case of identical (monozygotic) triplets, two of whom have agenesis of the corpus callosum, is presented. Prenatal ultrasonography and magnetic resonance imaging revealed two of the triplets to have agenesis of the corpus callosum and the third triplet to have an intact corpus callosum. No such case has been reported in the literature. Theories of the etiology and pathogenesis of corpus callosum agenesis are discussed. In this case, unequal X-inactivation as related to the twinning process is implicated as the cause of the agenesis.

KEY WORDS • corpus callosum agenesis • genetic predisposition • X-inactivation • multiple gestation

Agenesis of the corpus callosum is a congenital abnormality estimated to occur in one to three births per 1000.9,19 The etiology and pathogenesis of agenesis of the corpus callosum is unclear. Agenesis of the corpus callosum may occur as an isolated anomaly without apparent clinical effect, or more commonly, as part of a syndrome.22 The group of defects most commonly associated with agenesis of the corpus callosum are the holoprosencephaly series. Associated cerebral abnormalities include porencephaly, encephalocele, microcephaly, pyramidal tract anomalies, and, rarely, hydrocephalus. Agenesis of the corpus callosum is generally believed to occur sporadically, although several familial cases have been reported. Published familial cases have noted autosomal-dominant, sex-linked recessive, and most frequently autosomal recessive inheritance.

We present a case of identical (monozygotic) triplets, two of whom have agenesis of the corpus callosum. This family was studied closely to provide insight into the possible cause of agenesis of the corpus callosum. The literature is also reviewed with respect to the pathogenesis of agenesis of the corpus callosum.

Case Report

History. These identical (monozygotic) female triplets were delivered by Caesarean section at 30 weeks gestation to a 33-year-old Caucasian mother because of premature labor. Pregnancy was complicated by first trimester hyperemesis requiring hospitalization and the use of thorazine suppositories, and a first trimester urinary tract infection that was treated with cephalaxin. The mother, experiencing her third pregnancy, had no difficulty conceiving. She had had two elective abortions. There was no family history of multiple births. Initially, there was no reported family history of genetic disorder; however, both the mother and all three children were later diagnosed with Von Willebrand disease.

Prenatal Ultrasonography. Prenatal ultrasonography revealed mild-to-moderate ventricular dilation of the cerebral ventricles of triplets B and C. Prenatal ultrasonography obtained in triplets B and C also revealed typical agenesis of the corpus callosum, including ventricular dilation consistent with colpocephaly and widely separated small frontal horns of the lateral ventricles. Magnetic resonance (MR) imaging confirmed the diagnosis of agenesis of the corpus callosum in triplets B and C.

Postnatal Diagnosis. Later MR imaging in triplet A revealed intact corpus callosum with no evidence of hydrocephalus (Fig. 1).

Genetic Analysis. The children are identical triplets; this was confirmed by DNA fingerprinting. The interconnected placenta showed no evidence of any abnormalities or areas of infarction. The placenta was monochorionic diamniotic. Monochorionic multiple births produce identical offspring.11 Because there were two amnions, two of the three fetuses occupied the same amnion.

Operations. Triplets B and C, between the ages of 2 and 3 years, had bilateral ventriculoperitoneal shunts placed because of expanding head circumference, increased ventricular size, and developmental delay. There was some
improvement in both children after shunting. Triplet B began to walk, use both hands independently without bias, and sleep in a more normal pattern. Triplet C had a shunt-related subdural hematoma and required upgrading of the shunt with an antisiphon device and subdural peritoneal shunt placement. After surgery, triplet C became more verbal.

Postoperative Course. The triplets are 7 1/2 years old at the time of this publication and are quite active and continue to thrive, although with significant developmental delays. Triplets B and C are reported to have intelligence quotients of 50 and 65, respectively. They have a limited vocabulary and tend to use hand gestures and signs more than words. They continue to improve and respond to the physical and occupational speech therapies in which they are participating. All three children have been diagnosed with attention deficit disorder and are being treated with Ritalin. Triplet A has been reported to have some mild degree of difficulty in school, but is otherwise normal.

Discussion

Investigators have been exploring the causes of agenesis of the corpus callosum since 1872. Primary agenesis is the result of early embryonic defect of the lamina terminalis or faulty migration of cells during the early development of the corpus callosum. Secondary agenesis of the corpus callosum is the result of injury (inflammation, hydrocephalic, or porencephalic processes) or obstruction (tumor) to the already developed corpus callosum in later fetal life. The unique case of identical triplets, two of three affected with agenesis of the corpus callosum and hydrocephalus, allows comment on the possible primary abnormality involved in the formation of the corpus callosum.

An important structure in the early development of the corpus callosum is the lamina terminalis. The lamina terminalis is divided into a telencephalic or dorsal portion and a diencephalic or basal portion and is derived from the closure of the anterior neuropore. The dorsal lamina terminalis contains the anterior commissure, corpus callosum, commissural fornices, septum telencephalic, and the subfornical organ. The basal portion of the lamina terminalis goes on to form the rostral wall of the preoptic recess and the supraoptic crest.

The corpus callosum originates as fibers that cross the midline through the commissural plate (dorsal portion of the lamina terminalis). This plate, first seen around Day 39, allows for the axons to cross the midline. As the neuronal fibers grow they extend superiorly and caudally, producing the crescent-shaped adult corpus callosum. The formation of the corpus callosum begins approximately the 12th week of gestation and is complete at 20 weeks of gestation.

Four main theories have been proposed to explain the etiology of agenesis of the corpus callosum. Classic agenesis of the corpus callosum is thought to occur because of failure of the callosal fibers to cross the midline. Here the problem lies not in the development or growth of the callosal fibers but in their inability to traverse the midline. It has been demonstrated in mice and in hamsters that surgical interruption of the callosal plate leads to callosal agenesis.

The second theory of agenesis of the corpus callosum postulates pathology of the anterior neuropore closure. Improper or failed closure could subsequently lead to the absence of the lamina terminalis, ensuing commissural plate and, thus, the development of agenesis of the corpus callosum.

A third theory involves migrational arrest of callosal neurons. Two anomalies that may be associated with such disruptions are lissencephaly and schizencephaly. In Type II lissencephaly, hydrocephalus is commonly present. The existence or extent of such a relationship is not known. Embryologically, migrational arrest occurs in Type I lissencephaly at the same time (12–16 weeks of gestation) as callosal crossing. Sometimes in severe forms of agenesis of the corpus callosum callosal neurons totally miss their target cells.

The fourth theory postulates that agenesis of the corpus callosum

FIG. 1. Magnetic resonance T1-weighted imaging in triplets at age 5 years. Sagittal (A) and coronal (B) images in triplet A demonstrating intact corpus callosum. Sagittal (C) and coronal (D) images in triplet B and sagittal (E) and coronal (F) images in triplet C demonstrating complete agenesis of the corpus callosum.
callosum is the result of an interruption in corpus callosum maturation. Such a disruption would most likely occur in the second half of fetal life. Dysmyelination and atrophy of the corpus callosum can be caused by vascular lesions and hydrocephalus. Tumors may also result in the partial absence of the corpus callosum. In cases in which there is an arrest of corpus callosum development the result is most likely an incomplete or abnormal corpus callosum. On the other hand, processes that lead to total agenesis of the corpus callosum generally result from early embryonic insult.

The etiology of agenesis of the corpus callosum, particularly sporadic cases, remains unknown. In some cases the etiological factors seem clear; however, in most cases, agenesis of the corpus callosum appears in combination with many malformations occurring in associated syndromes. Often the link between these malformations and agenesis of the corpus callosum is the time of embryonic insult. To date there are several apparent etiological causes for agenesis of the corpus callosum including toxic–metabolic causes, chromosome anomalies, single gene abnormalities (X-linked dominant and recessive, autosomal recessive, and familial heredity), vascular causes, infection, and x-ray exposure. Although agenesis of the corpus callosum is a frequently reported malformation of the central nervous system, the situation becomes unique when it involves children of multiple births. The birth of triplets is a rare event. This case is the first to report agenesis of the corpus callosum and hydrocephalus in two of three monozygotic triplets. Triplets may be trizygotic, dizygotic, or monozygotic. Trizygotic triplets stem from fertilization of three different ova. Dizygotic triplets are derived from two eggs from either one or both ovaries, one of which splits after fertilization. In monozygotic conceptions, a single fertilized ovum divides and produces an embryonic mass of cells. Ordinarily this would develop into a single embryo, but occasionally, this mass subdivides into two masses, each developing into an embryo. In triplets, one of the two masses splits once more to form a total of three genetically identical embryos. Because these three embryos stem from one ovum, the genetic material is identical in most cases (Fig. 2). However, discordance between monozygotic children as a result of variations in environment, before and after birth, has been reported. The differences include more favorable fetal position, better blood supply, postnatal infection or even gene mutations, and chromosomal aberrations. In fact a relationship between twinning, neural tube anomalies, and unequal X-chromosome inactivation was suggested by Burn, et al. 

The Lyon hypothesis states that in females one X chromosome is inactivated at random in each cell, leaving only one X chromosome active (X-inactivation). All cells stemming from such a cell would maintain the same inactive X chromosome. The phenomenon of X-inactivation is essential; otherwise females (XX) would have a “double...
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The inactive X chromosome forms the Barr body. Because of the normally random nature of X-inactivation, it can be said that heterozygotic females are genetic mosaics in whom some patches of somatic tissue have the paternal X chromosome active and others the maternal.

Burn, et al., hypothesized that random X-inactivation resulted in two contrasting cell masses with either maternal or paternal X-inactivation. This segregation was then followed by, and may have resulted in, monozygotic twinning. This suggests that uneven X-inactivation in female monozygotic twins may be directly related to the twinning process (Fig. 3). The twinning process and lyonization may be related such that one event may lead to the other. In most monozygotic twins the splitting occurs at 3 to 8 days postfertilization. Random X-inactivation in mammals occurs early in embryonic development at approximately 8 to 10 days postfertilization (blastocyte stage). Although the exact mechanisms and time of X-inactivation are not completely understood, it is clear that X-inactivation occurs at a sufficiently early stage to influence the phenotype of females developed from later monozygotic twinning processes.

There are two mechanisms by which uneven or skewed X-inactivation might be the underlying method for agenesis of the corpus callosum expression in the two affected children. In both, agenesis of the corpus callosum expression is most likely due to the X-inactivation of the X chromosome carrying the normal gene. More specifically, the two affected children could have an inactivated X-linked gene for callosal development whereas their normal sister received an active (normal) X chromosome. The exact method of agenesis of the corpus callosum expression differs depending on whether X-inactivation occurred before or after the twinning process (Figs. 4 and 5).

Previous literature has reported 16 cases of skewed inactivation in monozygotic twins discordant for an X-linked trait. In one pair, the normal twin had a random inactivation, whereas her affected sibling had skewed inactivation toward the normal X chromosome. In four similar pairs the normal siblings were skewed toward the mutated X chromosome.

At the appropriate time in embryogenesis, X-inactivation occurs to affect the twinning process. Because these three girls have identical genes, nonrandom (unequal) X-inactivation offers a plausible explanation as to why two of the three developed agenesis of the corpus callosum. Further genetic testing is required for confirmation.
References


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