

X linked recessive inheritance of agenesis of the corpus callosum

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SUMMARY A 2-year-old boy with psychomotor retardation, congenital unilateral ptosis, bilateral adducted thumbs, weakness of upper limbs, and Hirschsprung's disease (aganglionosis), with complete agenesis of the corpus callosum and hypoplasia of the inferior vermis and cerebellum is reported. His 24-year-old maternal uncle, with severe psychomotor retardation but none of the other physical problems, also has agenesis of the corpus callosum demonstrated by CT scan. The implications for antenatal diagnosis are discussed.

Agenesis of the corpus callosum may occur alone or as part of a syndrome. A small proportion of cases of agenesis of the corpus callosum are familial.¹ Most of the recurrences occur in sibs suggesting autosomal recessive inheritance. In only two reported kindreds is there evidence of X linked recessive inheritance.^{2,3} There is great clinical variability, both intrafamilial and interfamilial. The pathogenesis of agenesis of the corpus callosum is not well understood but is thought to result from faulty migration of cells. Often it is associated with other cerebral anomalies such as heterotopias, microgyria, lissencephaly, schizencephaly, and abnormalities of the pyramidal tract. It may be these abnormalities that cause the clinical symptoms rather than the absence of the corpus callosum as the latter has been found in asymptomatic persons.⁴ The fibres of the corpus callosum first appear at 74 days of gestation. By 115 days development is complete. This allows the possibility that agenesis of the corpus callosum may be detected by ultrasonographic techniques at the 16th week of gestation.

The purpose of this paper is to describe another family with psychomotor retardation and agenesis of the corpus callosum with evidence of X linked recessive inheritance.

Case reports

CASE 1

The proband is a 2-year-old boy born to a 25-year-old primigravida mother and a 27-year-old father. The parents are non-consanguineous Ashkenazi Jews. During the first trimester the mother had slight

vaginal bleeding but the rest of the pregnancy was uneventful. The proband's birth weight was 3.09 kg (25th centile), length was 49 cm (10th centile), and head circumference was 33.5 cm (10th centile). At birth he was noted to have bilateral adducted thumbs, clinodactyly of the second and fourth fingers, weakness of the shoulder girdle, and ptosis of the right upper eyelid. The cranial nerves were normal. At 24 hours of age, he developed signs of Hirschsprung's disease.

At present, he remains normocephalic (10th centile), his length and weight are on the 10th centile, and he is handsome. Psychomotor development has been delayed throughout. He has not had any seizures, nystagmus, or ataxic movements. Reflexes are normal.

CT scan of the brain showed prominent cerebrospinal fluid spaces and slightly enlarged ventricles, consistent with delayed brain growth. The third ventricle was high and interposed between the lateral ventricles, signs compatible with agenesis of the corpus callosum. The cisterna magna and fourth ventricle were large, indicating hypoplasia of the inferior vermis and cerebellum.

The electroencephalogram was abnormal, with poorly organised background activity and anterior projection of theta activity.

CASE 2

This 24-year-old man is the maternal uncle of case 1. He has marked psychomotor retardation and is unable to walk or speak. His head circumference is 52 cm (3rd centile). He has speckled irides and pectus excavatum but no ptosis, adducted thumbs, Hirschsprung's disease, or seizures. CT scan showed

absence of the corpus callosum with an intact cerebellum.

FAMILY DATA

The proband's mother has two other brothers who are normal. A third cousin (maternal) had Hirschsprung's disease. CT scan of the mother's brain was normal. Chromosome analyses (Giemsa banding and with folic acid deprived medium) were normal in the proband, his mother, and her affected brother.

Because of the possibility that this syndrome of retardation and agenesis of the corpus callosum has been inherited in an X linked recessive manner, antenatal diagnosis was offered for the subsequent pregnancy. With ultrasonography at 16, 18, and 20 weeks, there was no evidence of absent corpus callosum and a normal female karyotype was obtained on amniocytes.

Discussion

The corpus callosum is the largest fibre tract in the brain and connects the two hemispheres; its absence may present as 'interhemispheric disconnection'. However, absence of the corpus callosum alone may not cause symptoms. Many cases of agenesis have been identified incidentally at necropsy in people who had normal cerebral function. Agenesis of the corpus callosum occurs in many different syndromes and does not cause a pathognomonic phenotype. These syndromes usually occur sporadically but there are at least 14 reports of familial involvement.¹

In most of the families, analysis of the pedigrees is compatible with autosomal recessive inheritance. Andermann⁵ reported a large French Canadian kindred in which 177 people in 108 sibships had a syndrome of agenesis of the corpus callosum, flaccid quadriplegia, areflexia, and psychomotor retardation. In this kindred there was a high rate of parental consanguinity, with one ancestral couple from the 17th century common to many affected people, there were many sibs involved, and there were no direct ascendants affected, all of which support autosomal recessive inheritance.

Autosomal dominant inheritance has been noted in one family in which a father and son had agenesis of the corpus callosum and megalencephaly.⁶ The son had trouble in reading but showed minimal inter-hemispheric disconnection. The daughter, who also had school problems, had slight right hemispheric dysfunction but was normocephalic and had a normal CT scan.

X linked dominant inheritance has been one of the postulated modes of inheritance for the Aicardi syndrome of agenesis of the corpus callosum,

psychomotor retardation, seizures with EEG changes of hypsarrhythmia, chorioretinal lacunae from depigmentation, and other abnormalities. Our patients do not have the chorioretinal or dysmorphic features of this syndrome. It usually involves females only, although an affected male has been reported, but there are no familial cases.

In only two reports^{2,3} is there evidence of X linked recessive inheritance. In one family, reported by Menkes *et al.*,² five males (two brothers, their half brother, a maternal uncle, and a maternal cousin) began convulsing in the newborn period. They were severely retarded and three died in infancy. Two half brothers and their cousin had either partial or complete agenesis of the corpus callosum. Polymicrogyria and heterotopias were also present. The other two males did not have diagnostic tests. Opitz and Kaveggia³ reported a family of three brothers and their two maternal male cousins with megalencephaly, hypotonia, imperforate anus, and other non-specific abnormalities. One boy had absence of the posterior third of the corpus callosum, another had a normal brain at necropsy, and the remainder were not investigated. There is a suggestion of X linked recessive inheritance in the family reported by Ziegler,⁷ where all three brothers had a clinical course similar to that of Menkes' family. Only two of these had agenesis of the corpus callosum. None of the mother's three brothers or three half brothers was affected so there is no definite evidence for X linked recessive inheritance.

Agenesis of the corpus callosum has been an occasional feature in several well-delineated autosomal dominant and recessive syndromes, in sporadic syndromes, and in various chromosomal syndromes (trisomy 18, 13, 8, F; 4p—, XO, XXY, translocations).

It is apparent that there is great variability in the clinical presentation both within and among the families with syndromes involving the corpus callosum. Seizures, psychomotor retardation, hypotonia, hydrocephalus, visual problems, and short stature have been described. Malformations involving every system of the body have been observed. The variability in neurological signs is probably the result of the other cerebral anomalies frequently associated with agenesis of the corpus callosum. Abnormalities of the forebrain result in heterotopias, microgyria, absent olfactory tract, porencephalic cysts, hydrocephalus, diencephalic cysts, and fusion of the thalami and mammillary bodies. Mid-brain angiomas and dysgenesis of the hind-brain, cerebellum, and spinal cord occur. There may be abnormal decussation of the pyramidal tract and absent cranial nerves.⁸ Besides the incidental findings at necropsy mentioned previously, it was

noted that in several sibships of children with agenesis of the corpus callosum there were sibs with identical problems such as seizures and psychomotor retardation, yet not every affected child had agenesis of the corpus callosum.^{7,9} The proband in this report had cerebellar and inferior vermis hypoplasia, ptosis, adducted thumbs, and weakness in the shoulders. These did not occur in his uncle, although both have agenesis of the corpus callosum.

In this family X linked recessive inheritance is the most likely mode of inheritance. It cannot be assumed, however, that another affected male relative would also have agenesis of the corpus callosum because of the previously mentioned affected sibs, only some of whom had absence of the corpus callosum, and because the absent corpus callosum may not be the cause of the cerebral dysfunction.

Nevertheless, since it now seems possible to detect agenesis of the corpus callosum by ultrasound at the 20th week of gestation, we would offer antenatal diagnosis for subsequent pregnancies of this mother, with sex determination of the fetus and ultrasound examination. The parents, before deciding to proceed, would be advised that a normal ultrasound examination of the fetal brain would not guarantee normality.

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