Mild fetal cerebral ventriculomegaly as a prenatal sonographic marker for Kartagener syndrome

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INTRODUCTION
Primary ciliary dyskinesia (PCD), also referred to as immotile-cilia syndrome or Kartagener syndrome, is a group of genetic disorders caused by defective cilia leading to chronic sinupulmonary infection, situs inversus and reduced fertility. Some PCD patients also have cerebral ventriculomegaly or hydrocephalus.

We report here two fetuses and one newborn with mild cerebral ventriculomegaly and a suspected and/or confirmed diagnosis of PCD. These cases demonstrate that mild fetal cerebral ventriculomegaly can be a prenatal sonographic marker of PCD, certainly in fetuses with situs inversus or a history of a previous sib with PCD. Copyright © 2003 John Wiley & Sons, Ltd.

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cerebral ventriculomegaly or overt hydrocephalus has also been described in dogs (Edwards et al., 1989; Dhein et al., 1990; Daniel et al., 1995), Wic-Hyd rats (Torikata et al., 1991; Shimizu and Koto, 1992; Nakamura and Sato, 1993), Hpy/Hpy mice (Bryan, 1983), mice with targeted disruption of the foxj1 gene (Chen et al., 1998) and mice with an insertional mutation in the axonemal dynein heavy-chain gene, Mdnah5 (Ibañez-Tallon et al., 2002). This suggests a functional role in liquor circulation for the cilia lining the ventricular ependyma of the brain and spinal cord in humans and other species.

Prenatal diagnosis of PCD is sometimes possible by mutation analysis of one of the genes currently known to be involved in PCD (Pennarun et al., 1999; Guichard et al., 2001; Olbrich et al., 2002). However, in the majority of cases, fetal ultrasound examination is the only method to detect PCD prenatally, if at least detectable structural anomalies such as situs inversus are present. However, half of the patients with PCD do not show situs inversus. As ventriculomegaly or hydrocephalus is sometimes present in neonates or children with PCD, it might offer an additional prenatal sonographic marker for PCD.

We present here two fetuses and one newborn with a suspected and/or confirmed diagnosis of PCD presenting with mild cerebral ventriculomegaly.

CASE REPORTS

Family 1
The healthy parents of family 1 were of Caucasian descent and unrelated (Figure 1). They were referred to our centre for prenatal diagnosis in their third pregnancy because of a previous child (II-2) with a primum atrial septal defect, aortic isthmus stenosis, absent right superior vena cava and a persistent left superior and
inferior vena cava connected to the coronary sinus. The congenital heart malformations did not necessitate surgical repair. Case II-2 had recurrent atelectases of the right lung and mildly dilated lateral cerebral ventricles in the neonatal period, both of which disappeared later on. However, he had frequent upper-airway infections during his childhood. Occipitofrontal circumference and mental development were normal at the age of five years. The diagnosis of PCD was not made until a suspicion of PCD in the next pregnancy. In that pregnancy (II-3), a fetal anomaly scan at 19 weeks revealed a right-sided stomach and a central liver, a primum atrial septal defect and a persistent left superior vena cava. There also existed mild cerebral ventriculomegaly, with the width of the posterior horn of the lateral ventricle measuring 13 mm (normal upper limit: 10 mm). Amincicentesis revealed a normal female karyotype, and a 22q11 deletion was excluded. PCD was suspected in sib II-2 in view of these ultrasound abnormalities and the presence of similar features with frequent upper-airway infections. After counselling, the parents decided to continue the pregnancy. At 37 weeks, a girl weighing 2750 g was born with Apgar scores of 6 (1′) and 8 (5′). The prenatally diagnosed cardiac abnormalities were confirmed, and in addition an absent inferior vena cava with azgyous continuation was found. Abdominal abnormalities included a right-sided stomach, septated spleen with a small accessoroy spleen, central position of the liver with drainage of the left hepatic veins into a persistent left inferior vena cava and intestinal malrotation with volvulus. The child suffered from respiratory difficulties, and atelectases of the lung developed. An ultrasound of the brain made in the first week of life showed cerebral ventricles within the normal size range. In view of the combination of cardiac and abdominal features compatible with a situs abnormality, neonatal lung atelectases and fetal and/or neonatal cerebral ventriculomegaly in one or both sibs, the diagnosis of PCD was suspected. Electron-microscopic examination of a nasal biopsy showed ciliary aplasia in both infants (II-2 and II-3), confirming the diagnosis of PCD. The first child (II-1) and the parents were healthy, but were not further investigated.

Family 2

A consanguineous couple (first cousins) of Moroccan descent was referred in the 10th pregnancy to our centre for prenatal diagnosis because of a previous child (II-6) with KS (Figure 1). The second child (II-2) died on day 2 after birth because of meconium aspiration, but...
DISCUSSION

We describe here two families with probable autosomal recessive PCD associated with mild ventriculomegaly. In the first family, both sibs affected with PCD had mild dilatation of the lateral cerebral ventricles. In the second family, PCD was suspected in two sibs, of which one showed mild fetal ventriculomegaly, and was confirmed in two additional sibs. In all three cases, cerebral ventriculomegaly was mild, and was only retrospectively recognised to be a part of PCD. The ventricular dilatation in PCD is probably due to a dysfunction of the cilia that line the ventricular ependyma of the brain and spinal cord. It has not only been described in humans but also in dogs, rats and mice with PCD. Consequently, the beating of these cilia must be important in the circulation of liquor. Mild fetal ventriculomegaly can be caused by many factors leading to parenchymal loss of abnormal cerebrospinal-fluid circulation. When diagnosed, additional prenatal tests (amniocentesis for karyotyping and virological studies, maternal platelet counts and virology) should be performed. As illustrated here, attention should also be paid to organ situs and structural heart defects in order to exclude PCD, certainly when a history of PCD in a previous child is present. Therefore, mild cerebral ventriculomegaly might be an early sign of PCD. This is important as PCD might be responsible for neonatal difficulties due to respiratory distress and/or meconium aspiration (Monnet, 1978; Whitelaw et al., 1981; Losa et al., 1995), or intestinal malrotation and/or congenital heart defects in case of situs ambiguus. To our knowledge, PCD has never been reported in post-natal follow-up studies of fetuses with mild cerebral ventriculomegaly (Bromley et al., 1991; Bloom et al., 1997; Vergani et al., 1998; Pili et al., 1999; Mercier et al., 2001; Kelly et al., 2001), probably because PCD is not always recognised in the neonatal period (Losa et al., 1995), particularly not in the absence of situs inversus. This highlights the importance of a thorough diagnostic evaluation of fetal and neonatal abnormalities. Furthermore, a careful family history can lead to an etiologic diagnosis that was not considered in individual affected family members, certainly in diseases with a clinical spectrum as variable as that of PCD.

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REFERENCES


