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BRIEF REPORT

# Unilateral multicystic dysplastic kidney in infants exposed to antiepileptic drugs during pregnancy

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**Abstract** Prenatal exposure to antiepileptic drugs (AEDs) increases the risk of major congenital malformations (MCM) in the fetus. AED-related abnormalities include heart and neural tube defects, cleft palate, and urogenital abnormalities. Among the various congenital anomalies of the kidney and urinary tract (CAKUT), multicystic dysplastic kidney (MCDK) disease is one of the most severe expressions. Although prenatal ultrasound (US) examination has increased the prenatal diagnosis of MCDK, the pathogenesis is still unclear. We report on four cases of MCDK in infants of epileptic women treated with AEDs during pregnancy. From October 2003 to June 2006, we observed four infants with unilateral MCDK born to epileptic women. Three patients were considered to have typical features of multicystic dysplastic kidney, and one infant was operated because of a cystic pelvic mass in the absence of a kidney in the left flank. The macroscopic appearance of this mass showed an ectopic multicystic kidney confirmed by histological findings. All patients have been studied by US scans, voiding cystourethrogram (VCUG), and radionuclide screening isotope imaging. The

prenatal exposure to AEDs increases the risk of major congenital malformations from the background risk of 1–2% to 4–9%. AEDs may determine a defect in apoptosis regulation that could lead to abnormal nephrogenesis, causing MCDK. Carbamazepine (CBZ) and phenobarbital (PHB) during pregnancy should be used at the lowest dosage compatible with maternal disease. The reduction, or even suspension, of drug dosage should be achieved from the periconceptional period to the first 8 weeks of gestation to avoid any interference with organogenesis.

**Keywords** Multicystic dysplastic kidney · Antiepileptic drugs · Major congenital anomalies · Infant

## Introduction

It is widely accepted that prenatal exposure to antiepileptic drugs (AEDs) increases the risk of major congenital malformations (MCM) in the fetus [1]. AED-related abnormalities include congenital midline heart defects, neural tube defects, cleft lip and palate, polydactyly, and urogenital abnormalities (hypospadias, duplex system, renal dysplasia, hydronephrosis) [2]. There is no evidence that infants born to untreated women with a history of epilepsy have an increased risk of MCM [3]. On the other hand, suspension of antiepileptic therapy may cause strong concern that the mother's seizures themselves could have a harmful effect on the fetus, including fetal bradycardia and mechanical consequences of maternal traumas [4]. Among the various congenital anomalies of the kidney and urinary tract (CAKUT), multicystic dysplastic kidney (MCDK) is one of the most severe expressions. Many teratogenic effects of AEDs are well described, but MCDK has not been reported in the literature. Although prenatal

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ultrasound (US) examination has increased the diagnosis of MCDK, the pathogenesis is still unclear. We report on four cases of unilateral MCDK in infants of epileptic women treated with AEDs during pregnancy.

### Patient reports

Our Institution is a level III referral center for high-risk pregnancies and newborns with congenital malformations in western Sicily. A mean of 950 prenatal US screenings are performed every year, with a mean of 40 US investigations per year in epileptic women. The incidence of isolated MCDK in western Sicily is 1.17/10.000 births [Indagine Siciliana Malformazioni Congenite (ISMAC) register for congenital malformations 2000–2005, personal data, not published]. In the last 36 months, we observed eight infants with unilateral MCDK. Four infants were born to epileptic women who underwent antiepileptic treatment with carbamazepine (CBZ) and phenobarbital (PHB) during pregnancy, and MCDK was diagnosed in utero with routine US scans. Amniocentesis, performed within 21 weeks of gestation, showed a normal karyotype in all patients.

All mothers started folic acid administration (5 mg per day) 1 month before pregnancy. No other risk factors such as smoking, alcohol, drugs, infections [toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex (TORCH)], abortions, hypertension, gestosis, diabetes, or other pharmacological treatments were present. For all women, the average daily dose of CBZ and PHB was 650 mg and 130 mg, respectively. Dose adjustment was made on a clinical basis to achieve the lowest dosage, especially during the first trimester of gestation. Three mothers underwent an elective cesarean section because of other reasons not related to epilepsy; one mother underwent urgent cesarean section because of evidence of fetal decelerations.

All newborns were delivered at term and had a birth weight appropriate for gestational age. Clinical findings showed facial dysmorphic features as reported in Table 1.

Three patients showed typical US scan features of MCDK and, therefore, we chose a nonoperative approach with clinical and US follow-up monitoring. One infant was operated because of computed tomography (CT) evidence of a cystic pelvic mass in absence of kidney in the left flank. The macroscopic appearance showed an ectopic multicystic kidney confirmed by histological findings.

At birth, no newborns showed any AED intoxication, drowsiness, excitement, or insufficient milk intake. The Finnegan Score was normal. Cerebral, cardiac, and abdominal US scans were unremarkable. The studies at birth included voiding cystourethrogram (VCUG) showing a contralateral vesicoureteral reflux only in one patient. Renal US scans of all parents were negative. At 1 month of age, radionuclide screening isotope imaging provided the absence of function in the multicystic kidney, and abdominal US scans showed compensatory hypertrophy of the contralateral healthy kidney. At clinical follow-up, growth rates and neurobehavioral assessment were within the normal limits. Reabsorption of the cysts was noted in two patients, whereas the cystic content did not change at 1-year follow-up in one patient.

### Discussion

Women with epilepsy account for approximately 0.6% of all pregnancies [5]. There are approximately 1.1 million women of childbearing age in the United States with epilepsy [6]. The maternal use of AEDs during pregnancy is based on the assumption that seizures, especially first-trimester seizures, place mother and fetus at risk of hypoxia, acidosis, and injury from blunt trauma being more harmful than the drugs [7]. Unfortunately, the prenatal exposure to AEDs increases the risk of a MCM from the background risk of 1–2% to 4–9% [8]. The risk of congenital malformations has been associated with all the AEDs, but recent studies suggest differences in teratogenic effects between various AEDs. The teratogenic effect of valproic acid (VPA) has been well established, MCM

**Table 1** Clinical findings and 1-year follow-up in four infants

Case no.	Birth weight (g) and gestational age (wk)	Dysmorphic features	Renal features	One-year follow-up
1	28.00 37.5	Hypertelorism	Left multicystic dysplastic kidney	Cystic reabsorption
2	33.20 38.2	Hypertelorism, epicanthal folds, short nose with long filtrum	Left multicystic dysplastic kidney	Cysts did not change
3	31.60 38.0	Hypertelorism, epicanthal folds	Right multicystic dysplastic kidney	Cystic reabsorption
4	25.90 37.2	Epicanthal folds, prominent lips	Absence of the kidney in the left flank; ectopic multicystic kidney	Surgery intervention at birth

incidence being increased ten-fold in the offspring of VPA-treated pregnant women [9]. Therefore, CBZ and PHB represented the drugs of choice for the treatment of virtually all types of epilepsy in the last decade. Nevertheless, Matalon et al. [10] found that CBZ exposure during pregnancy increases the risk of MCM from 2.7% to 6.7%. Furthermore, a combination of CBZ with PHB is more teratogenic than CBZ therapy alone [11].

It has been supposed that a direct toxic action of reactive epoxides or free radicals start oxidative stress. Lindhout et al. [12] proposed a reduced activity of epoxide hydrolase, which is involved in the detoxification of epoxides produced in CBZ catabolism. There could be genetic differences in the prevalence of people with low activity of epoxide hydrolase, which may explain the different rates of CBZ-induced congenital anomalies. Among urogenital defects, the association between AED therapy during pregnancy and hypospadias has been reported [13]. There is less evidence about kidney involvement (hydronephrosis, renal dysplasia) [14] and prenatal AED exposure.

The pathway of AED damage on the developing kidney is not completely understood. Several hypotheses have been proposed regarding the ontogenesis of various forms of CAKUT. A well-orchestrated program of cellular proliferation, differentiation, and apoptosis has been demonstrated to be an essential component of normal kidney and urinary-tract embryonic development [15]. Different active signals (*pax-2*, *bcl-2*) are thought to promote nephrogenesis and induce renal dysplasia. *Bcl-2* is a protein normally expressed in developing kidney that protects cells from apoptotic death [16]. In transgenic mice, an overexpression of *bcl-2* leads to renal cystogenesis through a high apoptotic rate [17]. Homozygous null *bcl-2* mice develop renal cysts by increased apoptosis of metanephric blastema during embryonic kidney development [18]. Therefore, in *bcl-2* knockout mice, cystic renal formation may result from an inability of some renal cells to undergo terminal differentiation. Winyard et al. [19] demonstrated that apoptosis is prominent in undifferentiated cells around dysplastic tubules; on the other hand, apoptosis is rare in dysplastic epithelia, which are thought to be ureteric bud malformations. *Bcl-2* is consistently and ectopically expressed in dysplastic kidney epithelia. All these data suggest that cystic formation can be modulated by *bcl-2* overexpression or can result from a reduced ability of renal cells to achieve terminal differentiation. It has been shown that PHB increases *bcl-2* levels, leading to consistent reduction or suppression of programmed cell death [20, 21]. PHB therapy during pregnancy could lead to abnormal nephrogenesis causing MCDK through an abnormal regulation of *bcl-2*.

Questions still remain as to whether *bcl-2* involvement may explain the clinical observations of MCDK after

prenatal exposure to AEDs; nevertheless, apoptosis deregulation probably plays a role in the multifactorial processes that lead to MCDK. Even if the AED mechanism involved in renal dysplasia remains unclear, our clinical findings suggest an AED toxicity during prenatal development, an observation supported by typical dysmorphic features at birth. It is difficult to demonstrate a causal effect between an infant's MCM and AEDs exposure during pregnancy. We believe that the list of malformations associated with the use of AEDs is probably incomplete, because most studies did not detect uncommon defects. To our knowledge, this is the first report of MCDK associated with CBZ and PHB maternal exposure.

Epileptic women of childbearing age must be informed about the risks of anticonvulsant consumption during pregnancy, especially in the periconceptional period. Epileptic women who undergo a programmed pregnancy may reduce the teratogenic risk by the use of folate prior to conception and the use of AEDs in monotherapy, keeping dosage as low as possible during organogenesis. Although we still need more evidences to assess the precise risk of MCDK after antiepileptic treatment during pregnancy, we assume that in selected women, the ideal management may be to lower AED dosage prior to conception and possibly to suspend administration at least during the first 8 weeks of gestation in order to avoid any interference with organogenesis.

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