Pediatr Nephrol (2007) 22:1054–1057
DOI 10.1007/s00467-007-0446-x

BRIEF REPORT

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

**Maurizio Carta · Marcello Cimador · Mario Giuffrè · Maria Sergio · Maria Rita Di Pace · Enrico De Grazia · Giovanni Corsello**

Received: 25 October 2006 / Revised: 21 December 2006 / Accepted: 10 January 2007 / Published online: 20 February 2007


**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

M. Carta · M. Giuffrè · G. Corsello
UTIN e Pediatria, Università di Palermo,
Palermo, Italy

M. Cimador · M. Sergio · M. R. Di Pace · E. De Grazia
Unità di Chirurgia Pediatrica, Dipartimento Materno Infantile,
Università di Palermo,
Palermo, Italy

M. Carta (✉)
Dipartimento Materno-Infantile,
Università di Palermo,
Via Cardinale Rampolla 1,
90100 Palermo, Italy
e-mail: mauriziocarta@yahoo.it

## 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 (hypospadia, 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

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<br>37.5 | Hypertelorism | Left multicystic dysplastic kidney | Cystic reabsorption |
| **2** | 33.20<br>38.2 | Hypertelorism, epicanthal folds, short nose with long filtrum | Left multicystic dysplastic kidney | Cysts did not change |
| **3** | 31.60<br>38.0 | Hypertelorism, epicanthal folds | Right multicystic dysplastic kidney | Cystic reabsorption |
| **4** | 25.90<br>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 hypospadia 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.

## References


1. Holmes LB, Harvey EA, Coull BA, Huntington KB, Khoshbin S, Hayes AM, Ryan LM (2001) The teratogenicity of anticonvulsant drugs. N Eng J Med 344:1132–1138
2. Pennel PB (2004) Pregnancy in women who have epilepsy. Neurol Clin 22:799–820
3. Fried S, Kozer E, Nulman I, Einarson TR, Koren G (2004) Malformation rates in children of women with untreated epilepsy; a meta-analysis. Drug Saf 27:197–202
4. Canger R, Battino D, Canevini MP, Fumarola C, Guidolin L, Vignoli A, Mamoli D, Palmieri C, Molteni F, Granata T, Hassibi P, Zamperini P, Pardi G, Avanzino G (1999) Malformations in offspring of women with epilepsy: a prospective study. Epilepsia 40:1231–1236
5. Fairgrieve SD, Jackson M, Jonas P, Walshaw D, White K, Montgomery TL, Burn J, Lynch SA (2000) Population based, prospective study of the care of woman with epilepsy in pregnancy. BMJ 321:674–675
6. Yerby MS (2001) The use of anticonvulsants during pregnancy. Semin Perinatol 25:153–158
7. Stumpf DA, Frost M (1978) Seizures, anticonvulsants, and pregnancy. Am J Dis Child 132:746–748
8. Samren EB, van Duijn CM, Christiaens GCML, Hofman A, Lindhout D (1999) Antiepileptic drug regimens and major congenital abnormalities in the offspring. Ann Neurol 46:739–746
9. Wide K, Winbladh B, Kallen B (2004) Major malformations in infants exposed to antiepileptic drugs in utero, with emphasis on carbamazepin and valproic acid: a nation-wide, population-based register study. Acta Pediatr 93:174–176

10. Matalon S, Schechtman S, Godzweig G, Ornoy A (2002) The teratogenic effect of carbamazepine: a meta-analysis of 1255 exposures. Reprod Toxicol 16:9–17
11. Janz D (1994) Are anti epileptic drugs harmful when taken during pregnancy? J Perinat Med 22:367–375
12. Lindhout D, Hoppener RJ, Meinardi H (1984) Teratogenicity of antiepileptic drug combinations with special emphasis on epoxidation (of carbamazepine). Epilepsia 25:77–83
13. Arpino C, Brescianini S, Robert E, Castilla EE, Cocchi G, Cornel MC, de Vigan C, Lancaster PA, Merlob P, Sumiyoshi Y, Zampino G, Renzi C, Rosano A, Mastroiacovo P (2000) Teratogenic effects of antiepileptic drugs: use of an International Database on Malformations and Drug Exposure (MADRE). Epilepsia 41: 1436–1443
14. Hernandez-Diaz S, Werler MM, Walker AM, Allen A (2000) Folic acid antagonists during pregnancy and the risk of birth defects. N Eng J Med 343:1608–1614
15. Pope JC, Brock JW, Adams MC, Douglas Stephens F, Ichikawa I (1999) How they begin and how they end: classic and new theories for the development and deterioration of congenital anomalies of the kidney and urinary tract, CAKUT. J Am Soc Nephrol 10:2018–2028
16. Chandler D, El-Naggar AK, Brisbay S, Redline RW, McDonnel TJ (1994) Apoptosis and expression of the bcl-2 proto-oncogene in the fetal and adult human kidney: evidence for the contribution of bcl-2 expression to renal carcinogenesis. Human Pathol 25:789–796
17. Trudel M, Lanoix J, Barisoni L, Bloudin M, Desforges M, L'Italien C, D'Agati V (1997) C-MYC-induced apoptosis in polycystic kidney disease is Bcl-2 and p53 independent. J Exp Med 186:1873–1884
18. Sorenson CM, Padanilam BJ, Hammerman MR (1996) Abnormal postpartum renal development and cystogenesis in the bcl-2 (−/−) mouse. Am J Physiol 271:F184–F193
19. Winyard PJD, Risdon RA, Sams VR, Dressler GR, Woolf AS (1996) The PAX2 transcription factor is expressed in cystic and hyperprofilerative dysplastic epithelia in human kidney malformations. J Clin Invest 98:451–459
20. Worner W, Schrenk D (1996) Influence of liver tumor promoters on apoptosis in rat hepatocytes induced by 2-acetylaminofluorene, ultraviolet light, or transforming growth factor beta 1. Cancer Res 56:1272–1278
21. Sanders S, Thorgeirsson SS (1999) Phenobarbital promotes liver growth in c-myc/TGF-a transgenic mice by inducing hypertrophy and inhibiting apoptosis. Carcinogenesis 20:41–49