Editor's Note

This paper by Perez-Aytes and colleagues exemplifies the concept of the "astute clinician model" in the assessment of teratogenicity. The authors demonstrate the principle of drawing causal inference when an unusually rare exposure is associated with a particularly distinctive outcome. In this patient, the immunosuppressive agent mycophenolate mofetil (MMF) is associated with a recognizable phenotype, and the report adds to the existing evidence reviewed in their paper that MMF is indeed a human teratogen. This report brings the total number of infants with this recurrent pattern of microtia with or without orofacial clefts to six. As pointed out by Perez-Aytes et al., women who are taking MMF for any indication require counseling of the potential risks prior to pregnancy.

John C. Carey, MD
Editor-in-Chief

Clinical Report

In Utero Exposure to Mycophenolate Mofetil: A Characteristic Phenotype?

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Mycophenolate mofetil (MMF) is a widely prescribed immunosuppressive agent after solid organ transplantation. Potential teratogenic effects after in utero exposure to MMF in experimental studies and clinical observations in humans has been postulated in recent literature. However, a specific pattern of malformation has not been identified yet. We present a newborn patient, born to a recipient of renal transplantation, who became pregnant while taking MMF as immunosuppressive therapy. The newborn exhibited cleft lip and palate, bilateral microtia and atretic external auditory canals, chorioretinal coloboma, hypertelorism, and micrognathia. An extensive review of the literature documented six other cases with similar malformations after in utero exposure to MMF. A consistent pattern of malformations comprising cleft lip and palate, microtia and external auditory canals could be observed in five of the six cases. A different malformative pattern observed in one of the patients could be attributed to a different agent rather than MMF. The possible teratogenic effects of other immunosuppressive drugs, such as tacrolimus and prednisone, to which this patient was also exposed, are discussed herein. In addition, the differential diagnosis with other dysmorphic syndromes that can present with a similar phenotype, such as CHARGE syndrome, 18q deletion and hypertelorism-microtia-clefting (HMC) syndrome, is presented. We conclude that in utero exposure to MMF can cause a characteristic phenotype and propose the existence of a mycophenolate-associated embryopathy whose main features are: cleft lip and palate, microtia with atresia of external auditory canal, micrognathia and hypertelorism. Ocular anomalies, corpus callosum agenesis, heart defects, kidney malformations, and diaphragmatic hernia may be part of the phenotypic spectrum of MMF embryopathy. The human teratogenicity of MMF is reinforced by this report, and the current contraceptive recommendations about its use in fertile women are stressed. © 2007 Wiley-Liss, Inc.

Key words: mycophenolate mofetil; organ transplantation; teratogenesis; embryopathy

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INTRODUCTION

Mycophenolate mofetil (MMF), available under the commercial name of Cellcept®, is an effective immunosuppressive agent used to avoid organ rejection after solid organ transplants and in the therapy of autoinmmune diseases [Tendron et al.,

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2002]. Currently, organ transplantation has become a major activity within medical practice and Spain is a leader in this field [Matesanz, 2000]. It has been calculated that around 14,000 deliveries among organs transplanted women have been reported worldwide the vast majority of these pregnancies corresponding to recipients of renal transplantation [Davision and Baylis, 2002]. Initially, pregnancy was ill-advised in these women because the risk for mother and child, derived from transplantation as well as from the use of immunosuppressive drugs was unknown [McKay and Josephson, 2006]. However more recently the possibility of pregnancy may be considered after organ transplantation [McKay and Josephson, 2006; Ross, 2006]. In 2003, the American Society of Transplantation concluded that, if allograft function is stable and no rejection episodes have occurred, pregnancy is usually safe following the first year of a transplant [McKay and Josephson, 2006]. Immunosuppressive drugs such as prednisone, azathioprine, cyclosporine A, and tacrolimus, have been extensively used in transplant recipients, and their side-effects upon the fetus studied [Tendron et al., 2002]. Recently, however, new molecules, such as MMF and sirolimus, have acquireda major role in the immunosuppressive armamentarium, and an increasing use of MMF in the therapeutics protocols after renal transplantation has been observed [Tendron et al., 2002]. Experimental studies have demonstrated teratogenic effects in pregnant animals exposed to MMF [EMEA, 2007] and malformations in humans also have been documented in some cases [Tendron et al., 2002; Sifontis et al., 2006], and for these reasons MMF is considered a potential teratogenic drug and effective contraception measures are recommended when used in fertile women [Roche laboratories, 1998; Østensen et al., 2006]. Nevertheless, no specific pattern of malformation has been defined after in utero exposure to MMF.

We report on a woman with a renal transplant who become pregnant receiving immunosupression with MMF. After birth, the baby presented with a pattern of malformation, very similar to those described in previous reports after in utero exposure to MMF [Armenti et al., 2004; Le Ray et al., 2004; Sifontis et al., 2006; Tjeertes et al., 2007]. Altogether these reports support the existence of a characteristic phenotype associated with the teratogenic effect of MMF.

CLINICAL REPORT

Our patient is a female, first pregnancy of a 25-year-old Spanish woman which received her first renal transplant in 1997 overcoming severe renal insufficiency derived from late diagnosed vesico-ureteral reflux. In 2004 organ rejection was diagnosed and a second renal transplantation was performed. After this second transplantation, immunosuppressive therapy with tacrolimus (12 mg/day) and MMF (500 mg/day) was started. When she became pregnant 2 years later, she was under this regimen. At 10 weeks of gestation pregnancy was diagnosed, and MMF was discontinued while tacrolimus was maintained through the rest of pregnancy. Fetal ultrasound at 20 weeks of gestation showed the presence of cleft lip and palate. Amniocentesis was performed and a 46, XX normal female karyotype was diagnosed. After being informed, the mother decided to carry on with the pregnancy. At 41 weeks of gestation a female was delivered by caesarean (weight: 3,050 g; length: 52 cm; head circumference: 33.5 cm). Physical examination showed an active newborn with bilateral upper cleft lip with complete cleft palate, bilateral microtia, hypertelorism, micrognathia, and mild left ptosis (Fig. 1a,b). No other anomalies were observed. Ocular funduscopy showed a large chorioretinal coloboma in both eyes. CT-scan of the temporal bone showed bilateral absence of external ear canals and small tympanic cavities with abnormal auditory ossicles; semicircular ducts and other structures of internal ear appeared

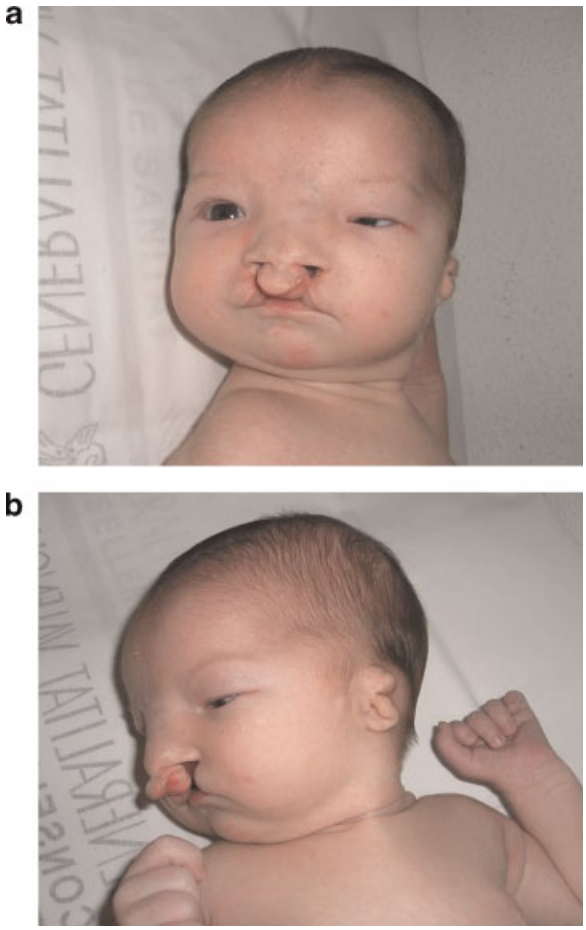

Fig. 1. **a**: Frontal view of the newborn presenting ptosis of the left eyelid, upper cleft lip, hypertelorism, and micrognathia. **b**: Lateral view of the newborn with microtia and with absence of the external auditory duct. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

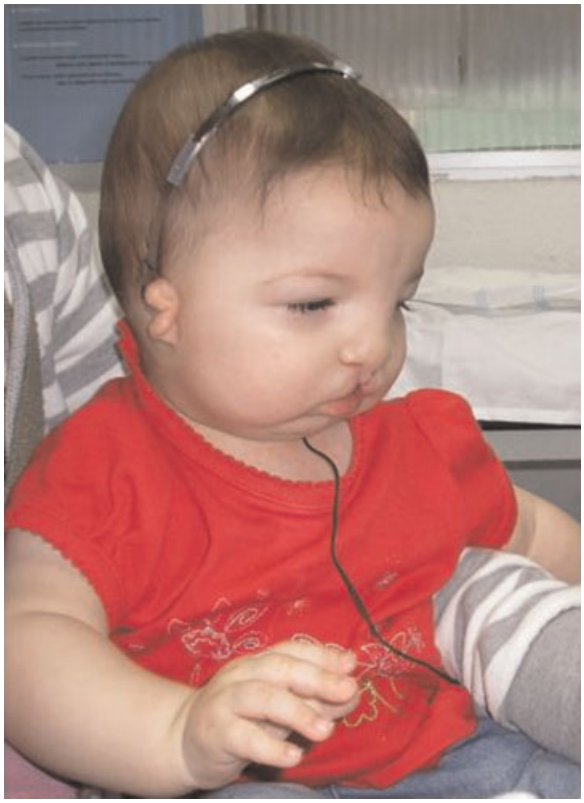

FIG. 2. Infant at 9 months of age wearing hearing aids. Cleft lip has been surgically repaired. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

normal. No anomalies were observed in CT-scan of brain and cerebellum. Results of both skeletal radiographs and abdominal ultrasound were normal. A 500 G-banded cytogenetic blood analysis showed a 46, XX normal female karyotype.

Cleft lip was repaired at 8 months and cleft palate repair is scheduled for the future. Bilateral conductive hearing loss was diagnosed after auditory evoked potentials exam at this age. At 9 months her weight was: 8.050 g (75th centile), length: 71 cm (50th centile), and OFC: 43 cm (25th centile). Although she needed hearing aids, her physical and neurodevelopment examination were normal for her age (Fig. 2).

DISCUSSION

The pattern of malformation exhibited by our patient has strong similarities with that observed in previous reports of infants with birth defects associated with maternal exposure to MMF [Pérgola et al., 2001; Armenti et al., 2004; Le Ray et al., 2004; Sifontis et al., 2006; Tjeertes et al., 2007]. The main clinical features of these cases are summarized in Table I. The first report with maternal use of MMF and newborn anomalies was by Pérgola et al. [2001]. These authors published the case of a 33-year-old woman, recipient of a second renal transplant when she was around 6–7 weeks of her third gestation. Two previous pregnancies, under a different immunosuppressive regimen (prednisone, cyclosporine, and azathioprine), resulted in two normal female babies. After this second transplantation, therapy with MMF, tacrolimus, and corticosteroids was initiated and maintained during the rest of gestation. The women also received antiinfective therapy with vancomycyn and cefepime, and antihypertensive therapy with nifedipine, this last medication was initiated before transplantation and discontinued by the third week posttransplant because of hypotension. Pregnancy was diagnosed at 26 weeks, and MMF dose was reduced from 2 to 1 g/day, and antibiotics suppressed, the authors calculated that she received MMF from 7 weeks gestation to the birth of the baby. At 34 weeks she delivered a 2,250 g female with hypoplastic finger and toenails and shortened fifth fingers bilaterally. On the follow-up, an aberrant blood vessel between trachea and esophagus was diagnosed. At age 3 years the child had normal development. Armenti et al. [2004], in a report from the U.S. National Transplantation Pregnancy Registry (NTPR), recorded 21 pregnancies in 13 female kidney recipients, who had been exposed to MMF during gestation. Pregnancies resulted in 11 spontaneous abortions and 10 live births, within the 10 live births, 2 newborns with birth defects were reported. The first was the newborn previously described by Pérgola et al. [2001], and the second was a 1,531 g newborn, born at 31 weeks to a mother who became pregnant under MMF, tacrolimus, and prednisone. At 24 weeks, organ rejection was diagnosed and antithymocyte globulin and sirolimus was added. After delivery cleft lip and palate and microtia, were reported in the newborn. No anomalies were reported in the remaining eight live births exposed to MMF in the NTPR report [Armenti et al., 2004].

An important report was that the Le Ray et al. [2004], that published the case of a 27-year-old primiparous woman, recipient of a renal transplant 2 years before. When she became pregnant, she was receiving immunosuppressive therapy consisting of MMF, tacrolimus, and prednisone. Pregnancy was diagnosed at 13 weeks and MMF was discontinued and replaced with azathioprine, while tacrolimus and prednisone were continued. Pregnancy surveillance with ultrasound examinations showed at 22 weeks of gestation multiple fetal malformations, including corpus callosum agenesis and cleft lip and palate. Normal male karyotype was seen in amniocentesis. The mother decided for termination of pregnancy and pathological examination was accomplished. The fetus had cleft lip and palate, hypertelorism, micrognathia, microtia, and external auditory atresia, corpus callosum agenesis, and left pelvic ectopic kidney. No anomalies were noted in limbs, thorax,

TABLE I. Clinical Reports of Fetal/Newborn Malformations Associated With Maternal Exposure to MMF During Pregnancy

	Organ transplant	Immunosuppression during pregnancy	Newborn	Pattern of malformation
Pérgola et al. [2001] [case 1 of Sifontis et al., 2006]	Kidney	Prednisone (25 mg/day) Tacrolimus (7 mg/day) MMF (2 g/day since 6–7 weeks until 26 weeks; 1 g/day thereafter until delivery)	NS 34 weeks 2,250 g	Hypoplastic finger and toenails. Bilaterally shortened fifth finger. Aberrant blood vessel between trachea and esophagus
Armenti et al. [2004] [case 2 of Sifontis et al., 2006]	Kidney	Prednisone Tacrolimus MMF (500 mg/day until 24 weeks) Sirolimus from 24 weeks to delivery Antithymocyte globuline (added at 24 weeks)	NS 31 weeks 1,531 g	Cleft lip and palate Microtia
Le Ray et al. [2004]	Kidney	Prednisone (15 mg/day) Tacrolimus (9 mg/day) MMF (500 mg/day until 13 weeks) Azathioprine (50 mg/day) from 13 weeks to delivery	Male 22 weeks (TOP)	Cleft lip and palate Microtia (bilateral) and external auditory canal atresia Micrognathia Hypertelorism Left pelvic ectopic kidney Agenesis of corpus callosum
Sifontis et al. [2006] (case 3)	Kidney	Tacrolimus Prednisone MMF (250 mg/day throughout pregnancy)	NS 35 weeks 2,155 g	Cleft lip and palate Microtia Congenital diaphragmatic hernia Congenital heart defect
Sifontis et al. [2006] (case 4)	Kidney	Tacrolimus Prednisone MMF (1,000 mg/day until 15 weeks)	NS 39 weeks 2,886 g	Microtia
Tjeertes et al. [2007]	Kidney	Tacrolimus MMF (during first trimester)	Male 35 weeks 2,330 g	Microtia and absence of external auditory canal right ear Hydrops fetalis
Present case (2007)	Kidney	Tacrolimus/12 mg/day MMF (500 mg/day until 10 weeks)	Female 41 weeks 3,050 g	Cleft lip and palate Microtia (bilateral) and external auditory conduct atresia. Micrognathia Hypertelorism Bilateral choreoretinal coloboma

MMF, mycophenolate; NS, sex not specified; TOP, termination of pregnancy.

abdominal, and genital organs. The authors reported that a subsequent pregnancy in this woman 1 year later, resulted in a 2,640 g live born boy without congenital malformations, interestingly in this second pregnancy the mother was administered azathioprine, tacrolimus, and prednisone with no MMF. Le Ray et al. [2004] concluded that the malformations observed in their patient were possibly due to MMF, given that the fetus was exposed to MMF during the organogenesis period, that reports from animals experiments had showed similar malformations, and that the other immunosuppressive agents received by the woman, azathioprine, tacrolimus, and prednisone, had not been associated with increased incidence of fetal anomalies.

A recent report from the U.S. NTPR [Sifontis et al., 2006] have added two new cases with congenital malformations associated with maternal exposure to MMF: Sifontis et al. [2006] review data of 26 pregnancies corresponding to 18 kidney recipients, all with exposure to MMF during gestation. There were 15 live births from these 26 pregnancies, and in four (26.7%) malformations were reported. Cases 1 and 2 were that previously reported by Pérgola et al. [2001] and Armenti et al. [2004], respectively. The cases 3 and 4 from Sifontis et al. [2006] were from mothers exposed to MMF at least during the first 15 weeks of gestation. In case 3 the malformations consisted of cleft lip and palate, microtia, congenital diaphragmatic hernia and heart defect; case 4 was reported to have microtia. Sifontis et al. [2006] concluded that a higher incidence of malformations was seen with MMF, and the presence of microtia in three of the four reported cases suggested a pattern of malformation.

Very recently, Tjeertes et al. [2007] have reported on a kidney-transplanted woman who became pregnant under MMF and tacrolimus therapy. MMF was maintained during the first trimester. This

woman also suffered from psychosis needing diazepam and haloperidol during gestation. At 35 weeks, a 2,330 g male newborn was delivered with clinical signs of hydrops (pleural effusion, ascites), and microtia of right ear. The newborn was pale and dyspneic, and a low blood count of hemoglobin/hematocrit was seen. Immune, metabolic, and infectious etiologies for fetal hydrops were excluded after extensive investigations. An echocardiography showed a normal cardiac structure, and cytogenetic study documented a normal 46, XY karyotype. In magnetic resonance (MRI) study absence of right auditory pathway was seen without other defects. Tjeertes et al. [2007] concluded that, after exclusion of other etiologies, the most likely cause of fetal anemia that led to hydrops was MMF, because myelosupression can occur with its use, and that the malformation of right ear could be related to MMF exposure because no significant risk for fetal malformation were associated with the other drug exposures during pregnancy.

Thus the significant observation in all the cases described previously, including our patient, is the constant feature in all (except one) of a well-defined craniofacial pattern of anomalies comprising cleft lip/palate and/or microtia. In the cases where thorough clinical descriptions were reported [Le Ray et al., 2004; Tjeertes et al., 2007, present case, 2007] external auditory canal atresia, hypertelorism, and micrognathia were also found as a constant features (Table I). In the case of Pérgola et al. [2001], a completely different pattern was seen, but as the own authors pointed out, distal digits deficiencies could also be related to the nifedipine exposure of the mother. Distal phalangeal defects after nifedipine maternal exposure has been observed in animals experiments [Danielsson et al., 1990]. One possible mechanism for these defects is a fetal vascular disruption induced by a decreased utero-placental blood flow secondary to maternal hypotension caused by this drug [Danielsson et al., 1990]. It is notable that in the patient of Pérgola et al. [2001] nifedipine was discontinued because the mother developed hypotension. In our patient, chorioretinal coloboma was seen in funduscopy examination. No ocular anomalies have been reported in humans observations, but teratological studies of MMF in rats and rabbits resulted in fetal malformations including anophtalmia [EMEA, 2007]. Thus, ocular anomalies could be part of the phenotypic spectrum of MMF-related anomalies. Other malformations observed in animals studies were agnathia, hydrocephaly, ectopic kidney, and diaphragmatic hernia [Cellcept, Roche laboratories, 1998].

It is noteworthy that micrognathia was observed in the report of Le Ray et al. [2004] and in our patient, the oral/palatal clefts, hypertelorism, microtia/external auditory agenesis, and ocular coloboma establishes a possible link between the use of MMF during pregnancy and a specific malformation pattern consisting of anomalies in structures derived from the frontal-nasal prominence and first pharyngeal arch [O'Railly and Müller, 1992]. MMF is rapidly converted to its biologically active form, mycophenolic acid (MA), by esterases in the liver [Sinclair and Baildon, 2006]. MA produces potent, noncompetitive inhibition, of inosine-5′-monophostate dehydrogenase (IMPDH) which blocks de novo synthesis of purine necessary for activation and proliferation of lymphocytes. However, effects in other cells pathways that require purine derivatives have been observed in animal studies [Sinclair and Baildon, 2006]. Thus, there could be a potential specific teratogenic effect of MA on embryological cells derived from frontonasal prominence and first pharyngeal arch.

It can be argued that malformations observed in patients summarized in Table I could be also related to the other immunosuppressive drugs received by the mothers, as tacrolimus and corticosteroids. The main review about teratogenic effects of tacrolimus was of the Kainz et al. [2000]. These authors analyzed retrospectively, data of 100 pregnancies from 84 women under tacrolimus therapy. There were 68 live births, and in four of them malformations were reported. One case was referred as alcoholic embryopathy, a diagnosis not related with the use of tacrolimus, and in the three other no consistent malformative pattern was observed. One newborn had meningocele, urogenital defects and umbilical hernia; one other had ear defect, cleft palate and hypospadia, and the last one had multicystic dysplastic kidney [Kainz et al., 2000]. Although prednisone intrauterine exposure has been related with a small increase in oral clefts, large studies have not found an increased risk of this malformation [Østensen et al., 2006] and at therapeutic doses its use in humans is considered to have a nonspecific teratogenic effect [Tendron et al., 2002; Østensen et al., 2006]. Thus, it seems logical to relate the malformative pattern observed in our patient with MMF exposure, a drug that have showed a risk of 26.7% of malformations in the last U.S.NTPR report [Sifontis et al., 2006] than with the other immunosupressors which have demonstrated to be relatively safe with no malformative pattern [Kainz et al., 2000; Tendron et al., 2002; Østensen et al., 2006].

Some syndromes share some malformations with our patient, and should be considered in the differential diagnosis. Chorioretinal coloboma and microtia can be both present in CHARGE syndrome [Sanlaville and Verloes, 2007]. Nevertheless microtia is not the typical external ear anomaly usually associated to CHARGE syndrome, being more typical the cup ear. Notwithstanding, external ear anomalies are considered minor signs in this syndrome [Sanlaville and Verloes, 2007]. On the contrary, ocular coloboma represents one of the three major signs

[Verloes, 2005]. The other two major signs of CHARGE syndrome, as choanal atresia and hypoplastic semicircular ducts [Verloes, 2005] were absent in our case. Particularly, hypoplastic semicircular canals, considered a very specific and constant anomaly in CHARGE syndrome [Sanlaville and Verloes, 2007] were not observed in our patient, thus we think that CHARGE syndrome is not probable in the present case.

Atresia of external auditory canal (aural atresia) is frequently observed in chromosome 18q deletion [Veltman et al., 2003] and a putative critical region for aural atresia has been located in 18q22.3 [Dostal et al., 2003]. In general, in 18q deletion syndrome, the size of the deletion correlates with the severity of the phenotype [Jones, 2006a] and we could expect a cytogenetically visible deletion in a patient with aural atresia associated to multiple congenital anomalies as is the case of our patient. No 18q deletion was observed in the chromosomal study in our patient. In addition, no chromosomal anomalies were observed in the case of Tjeertes et al. [2007], the other case where cytogenetical postnatal study was done.

Hypertelorism-microtia-clefting (HMC) syndrome (OMIM 239800) is a rare entity with nine cases reported in the literature [Amiel et al., 2001]. Autosomal recessive inheritance have been proposed but no genetic localization does exist for this syndrome that seems genetically heterogeneous [Amiel et al., 2001]. The three defining features of HMC syndrome are hypertelorism, microtia, and cleft lip/palate, all present in eight of the nine published cases [Amiel et al., 2001]. In our patient these three features were present, although other frequent features in HMC as large nasal tip, growth retardation and small head circumference [Amiel et al., 2001] were absent. Although mental retardation is a feature in HMC syndrome, normal psychomotor development have also been reported [Verloes, 1994; Amiel et al., 2001] as is the case of MMF patients of Pérgola et al. [2001], Armenti et al. [2004] (mentioned by Sifontis et al. [2006]), and our patient, all of them with normal development reported with more than 8 months of age. Chorioretinal coloboma has not been found in HMC syndrome [Amiel et al., 2001] but other features reported in MMF maternal exposure, as congenital heart defect and kidney malformation, are also part of phenotypical spectrum of HMC syndrome [Amiel et al., 2001]. Thus, phenotypical similarities seem to exist between HMC syndrome and MMF maternal exposure patients because both share hypertelorism, microtia and cleft lip/palate, the "core" of its clinical picture. Further definition of molecular genetics of HMC syndrome could dillucidate if MMF teratogenic effect produce a phenocopy of HMC syndrome, as it has been the case for other recognized teratogens as warfarin, that produce a phenocopy of X-linked recessive condrodysplasia punctata syndrome [Jones, 2006b].

In summary, a characteristic pattern of malformation after in utero exposure to MMF seems evident, and we propose the existence of a mycophenolate-associated embryopathy with the following main features: cleft lip and palate, microtia with atresia of external auditory canal, micrognathia, and hypertelorism. Ocular anomalies, corpus callosum agenesis, heart defects, kidney malformations, and diaphragmatic hernia, also could be part of the phenotypic spectrum. This evidence for this characteristic phenotype is supported by experimental studies in rats and rabbits where craniofacial malformations as microphthalmia and agnathia were observed [Cellcept, Roche laboratories, 1998; EMEA, 2007]. Psychomotor development seems favorable and normal growth has been reported in three patients [Pérgola et al., 2001; Sifontis et al., 2006, present case, 2007], although long-term follow-up is needed to confirm this. Finally, the human teratogenicity of MMF is reinforced by this report, and the current recommendations [Cellcept, Roche laboratories, 1998; Østensen et al., 2006] about its cautious use in women of childbearing years should be stressed.

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REFERENCES

Amiel J, Faivre L, Marianowskl R, Bonnet D, Couly G, Manach Y, Le Merrer M, Cormier-Daire V, Munnich A, Lyonnet S. 2001. Hypertelorism-Microtia-Clefting syndrome (Bixler syndrome): Report of two unrelated cases. Clin Dysmorphol 10:15–18.

Armenti VT, Radomski JS, Moritz MJ, Gaughan WJ, Hecker WP, Lavelanet A, McGrory CH, Coscia LA. 2004. Report from the national transplantation pregnancy registry (NTPR): Outcomes of pregnancy after transplantation. Clin Transpl 103–114.

CellCept®. 1998. Product information: Roche Pharmaceuticals.

Danielsson BRG, Danielsson M, Reiland S, Rundqvist E, Dencker L, Regard CG. 1990. Histological and in vitro studies supporting decreased uteroplacental blood flow as explanation for digital defects after administration of vasodilators. Teratology 41:158–193.

Davision JM, Baylis C. 2002. Renal disease. In: de Swiet M, editor. Medical disorders in obstetric practice 4e. Malden, MA: Blackwell Science. p 198–266.

Dostal A, Nemeckova J, Gaillyova R, Vranova V, Zezulkova D, Lejska M, Slapak I, Dostalova Z, Kuglik P. 2003. Identification of 2.3-Mb gene locus for congenital aural atresia in 18q22.3 deletion: A case report analysed by comparative genomic hybridisation. Otol Neurotol 27:427–432.

EMEA (European Medicines Agency). 2007. CellCept, European public assessment report 2007 (EPAR). http://www.emea.europa.eu/humandocs/Humans/EPAR/cellcept/cellcept.htm (consulted 03/07/07).

Jones KL. 2006a. Deletion 18q syndrome. In: Jones KL, editor. Smith's recognizable patterns of human malformation, 6e. Philapelphia: Elsevier Saunders. p 62–63.

Jones KL. 2006b. Fetal warfarine syndrome. In: Jones KL, editor. Smith's recognizable patterns of human malformation, 6e. Philapelphia: Elsevier Saunders. p 656–657.

Kainz A, Harabacz I, Cowlrick IS, Gadgil SD, Hagiwara D. 2000. Review of the course and outcome of 100 pregnancies in 84 women treated with tacrolimus. Transplantation 70:1718–1721.

Le Ray C, Coulomb A, Elefant E, Frydman R, Audibert F. 2004. Mycophenolate mofetil in pregnancy after renal transplantation: A case of major fetal malformations. Obstet Gynecol 103:1091–1094.

Matesanz R. 2000. El transplante de órganos sólidos en España: éxito de una política. Rev Clin Esp 200:157–162.

McKay DB, Josephson MA. 2006. Pregnancy in recipients of solid organs. Effects on mother and child. N Engl J Med 354:1281–1293.

O'Railly R, Müller F. 1992. Human embryology and teratology. New York: Wiley-Liss. 330 p.

Østensen M, Khamashata M, Lockshin M, Parke A, Brucato A, Carp H, Doria A, Rai R, Meroni P, Cetin I, Derksen R, Branch W, Motta M, Gordon C, Ruiz-Irastorza G, Spinillo A, Friedman D, Cimaz R, Czeizel A, Piette JC, Cervera R, Levy RA, Clementi M, De Carolis S, Petri M, Shoenfeld Y, Faden D, Valesini G, Tincani A. 2006. Anti-inflamatory and immunosuppressive drugs and reproduction. Arthritis Res Ther 8:209 (doi: 10.1186/ar1957).

Pérgola PE, Kancharla A, Riley DJ. 2001. Kidney transplantation during the first trimester of pregnancy: Immunosuppression with mycophenolate mofetil, tacrolimus, and prednisone. Transplantation 71:994–997.

Ross L. 2006. Ethical considerations of pregnancy in the female transplant recipient. N Engl J Med 354:1313–1316.

Sanlaville D, Verloes A. 2007. CHARGE syndrome: An update. Eur J Hum Genet 15:389–399.

Sifontis NM, Coscia LA, Constantinescu S, Lavelanet AF, Moritz MJ, Armenti VT. 2006. Pregnancy outcomes in solid organ trasplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 82:1698–1702.

Sinclair A, Baildon R. 2006. Mycophenolate mofetil: An overview. Lupus 15:70–78.

Tendron A, Gouyon JB, Decramer S. 2002. In utero exposure to immunosuppressive drugs: Experimental and clinical studies. Pediatr Nephrol 17:121–130.

Tjeertes IFA, Bastiaans DET, van Ganzewinkel CJML, Zegers SHJ. 2007. Neonatal anemia and hydrops fetalis after maternal mycophenolate mofetil use. J Perinatol 27:62–64.

Veltman JA, Jonkers Y, Nuijten I, Janssen I, van der Vliet W, Huys E, Vermeesch J, Van Buggenhout G, Fryns J-P, Admiraal R, Terhal P, Lacombe D, van Kessel AG, Smeets D, Schoenmakers EFPM, van Ravenswaaij-Arts CM. 2003. Definition of a critical region on chromosome 18 for congenital aural atresia by arrayCGH. Am J Hum Genet 72:1578–1584.

Verloes A. 1994. Hypertelorism-Microtia-Clefting (HMC) syndrome. Gen Couns 5:283–287.

Verloes A. 2005. Updated diagnostic criteria for CHARGE syndrome: A proposal. Am J Med Genet Part A 133A:306–308.