 American Journal of Medical Genetics Part A 146A:1963–1966 (2008)

Clinical Report

Mycophenolate Mofetil Embryopathy May Be Dose and Timing Dependent

Ghee Soon Ang,[1] Sheila A. Simpson,[2] and Aravind R. Reddy[1]*

[1]Department of Paediatric Ophthalmology, Royal Aberdeen Children's Hospital, Aberdeen, United Kingdom
[2]Department of Clinical Genetics, North of Scotland Regional Genetics Service, Aberdeen, United Kingdom

Received 13 February 2008; Accepted 15 May 2008

Mycophenolate mofetil (MMF) is an immunosuppressive agent that has now been recognized as teratogenic in humans. A pattern of malformations from in utero exposure to MMF has recently been described, and includes cleft lip and palate, microtia and atresia of the external auditory canal. We present a nulliparous mother who had taken MMF for recurrent erythema multiforme for the first 5 weeks of her pregnancy, and developed a spontaneous miscarriage during the seventh week of pregnancy. For her second pregnancy, she took MMF on her own accord for four days in the seventh week after her last menstrual period. The newborn had bilateral microtia, absence of the external auditory canals, and right iris and chorioretinal coloboma, consistent with the pattern recognized as part of the MMF embryopathy phenotype. As the newborn was not exposed to other immunosuppressive agents in utero, we believe that the phenotype described to be the result of the teratogenic effect of MMF. The spontaneous miscarriage in the first pregnancy may be due to the higher dose and longer duration of MMF exposure. The second pregnancy, with MMF exposure of 4 days, proceeded to term with the resultant phenotype. We conclude that the effect and severity of the embryopathy may be dependent on the dose, timing, and duration of MMF exposure. The manufacturer and the United States Food and Drug Administration have now disseminated information regarding the teratogenic risk of MMF. Women should be fully counseled and advised about contraception during the course of treatment with MMF. © 2008 Wiley-Liss, Inc.

Key words: coloboma; embryopathy; microtia; mycophenolate mofetil; teratogenesis

How to cite this article: Ang GS, Simpson SA, Reddy AR. 2008. Mycophenolate mofetil embryopathy may be dose and timing dependent. Am J Med Genet Part A 146A:1963–1966.

INTRODUCTION

Mycophenolate mofetil (MMF), an immunosuppressive agent, has recently been recognized as teratogenic in humans. A pattern of malformations from in utero exposure to MMF, which includes cleft lip and palate, microtia and atresia of the external auditory canal, has been proposed [Perez-Aytes et al., 2008]. We report on a woman who took MMF on her own accord for recurrent erythema multiforme for 4 days during the 7th week of her pregnancy. At birth, the baby presented with features consistent with the spectrum of the characteristic phenotype associated with in utero exposure to MMF.

CLINICAL REPORT

A 32-year-old nulliparous Caucasian woman initially developed erythema multiforme 2 years prior to her first conception, after taking trimethoprim for a urinary tract infection. Histopathologic assessment and immunofluorescence testing from the skin biopsy specimen confirmed the clinical diagnosis of erythema multiforme. Although responding well to oral prednisolone, the blistering erythema multiforme recurred every time the systemic corticosteroid was stopped. The virology titers were positive for herpes simplex virus, but high dose acyclovir did not prevent recurrence of her erythema multiforme.

Various steroid sparing agents, such as cyclosporin and azathioprine, were tried, but she was unable to tolerate the side effects. She was eventually placed on MMF, which was both effective and well tolerated

*Correspondence to: Aravind R. Reddy, Consultant Paediatric Ophthalmologist, Department of Paediatric Ophthalmology, Royal Aberdeen Children's Hospital, Westburn Road, Aberdeen AB25 2ZG, Scotland, United Kingdom. E-mail: aravind.reddy@nhs.net

DOI 10.1002/ajmg.a.32420

at 500 mg three times daily, when she inadvertently became pregnant. She stopped the MMF when she realized this, but by that time, she already had been on MMF for the first 5 weeks of her pregnancy. She suffered a spontaneous miscarriage at week 7 of her pregnancy.

As she did not develop any blisters after the miscarriage, she decided to start trying for a family 4 weeks later with her 36-year-old husband. However, within 2 months, the blisters recurred quite significantly. On her own accord, she took 500 mg MMF twice daily for 4 days in her 7th week of pregnancy (from the first day of her last menstrual period) before she realized that she was pregnant once more. She stopped the MMF immediately. Her pregnancy proceeded to term without any problems. She did not take any other systemic medication for her erythema multiforme during pregnancy.

The female baby was born at 40 weeks of gestation by spontaneous vaginal delivery, weighing 2,900 g at birth. There was no family history of any inherited disorders. Examination revealed an active newborn with bilateral microtia and no visible external ear canals (Fig. 1A). Ophthalmologic assessment revealed unilateral inferonasal iris and chorioretinal coloboma in the right eye (Fig. 1B). The left eye was normal. No other anomalies were observed, including cleft lip or palate. Magnetic resonance imaging (MRI) revealed normal cerebral and internal ear structures, but absent external auditory canals. The echocardiogram, renal sonogram, and vertebral radiographs were all normal.

The child has bilateral conductive hearing loss, for which she has a bone anchored hearing aid system. Her vision is excellent in both eyes (20/16 Snellen equivalent with Kay pictures), and she does not have any significant refractive error. Although she has not had formal psychometric testing, at age 3, her psychomotor, physical and visual development is progressing normally, with no obvious cognitive impairment.

DISCUSSION

MMF is an important immunosuppressive agent commonly used to prevent rejection of solid organ transplants and to treat autoimmune and inflammatory diseases. It is deesterified into mycophenolic acid, the active agent, which acts by noncompetitively blocking de novo guanine nucleotide production, thus inhibiting DNA and RNA synthesis during B and T lymphocyte proliferation and activation. MMF is generally considered to be relatively safe, and less likely to produce significant renal or hepatic toxicity. It is excreted in the urine, and has a plasma half life of around 16 hours [Bullingham et al., 1998]. Although not commonly used for erythema multiforme, it has been reported to be effective as an alternative treatment for recurrent disease, especially in patients dependent on corticosteroids [Davis et al., 2002].

There are several published articles on the potential teratogenic effects of MMF [Pergola et al., 2001; Le Ray et al., 2004; Sifontis et al., 2006; Tjeertes et al., 2007; Velinov and Zellers, 2008]. Velinov and Zellers [2008] reported a case where the mother had been taking MMF and adalimumab for lupus nephritis during the first 8 weeks of pregnancy. All the other cases reported maternal exposure to MMF and tacrolimus following renal transplantation. The duration of MMF exposure ranged from the initial 8 weeks to the full duration of the pregnancy. In common with the features described in these articles, our case had bilateral microtia. Only one other report described chorioretinal coloboma, which was found in both eyes [Perez-Aytes et al., 2008]. Our case had

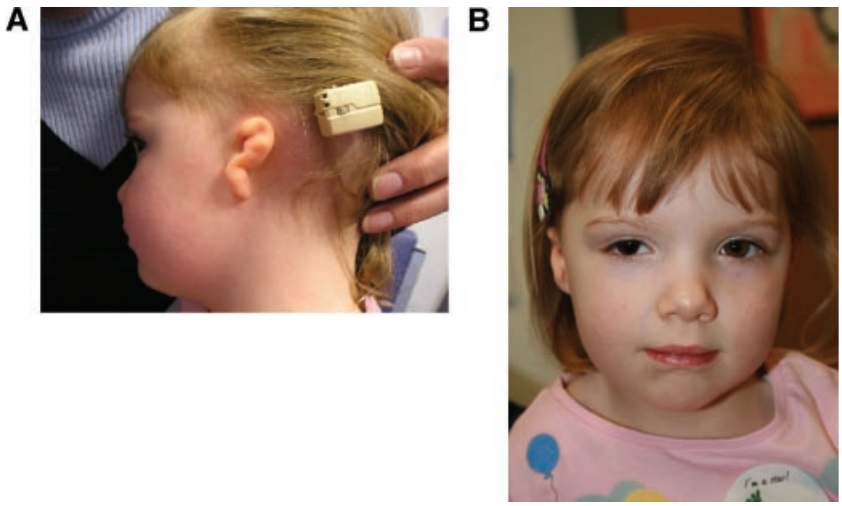

FIG. 1. **A**,**B**: The child at 3 years of age with the bone anchored hearing aid system, microtia, absence of the external auditory canals, and right iris coloboma.

unilateral iris and chorioretinal coloboma, but not cleft lip or palate.

Our case also differs from all previous reports in two important aspects. Firstly, maternal exposure was only to MMF, and no other immunosuppressive agent. This suggests that the anomalies seen are likely to have been due to MMF alone, and not due to another immunosuppressant, or any drug related interaction with MMF. There was no family history of any familial disorders. Other congenital conditions have to be considered as part of the differential diagnosis, including oculo–auriculo–vertebral (OAV) syndrome and CHARGE syndrome [Tasse et al., 2005; Stromland et al., 2007; Sanlaville and Verloes, 2007]. Ocular coloboma and microtia have been postulated to be present in a rare autosomal dominant subgroup of the OAV spectrum [Beck et al., 2005]. However, sporadic ocular coloboma and microtia, such as that seen in our patient, are uncommon in both the OAV spectrum and the CHARGE syndrome. Furthermore, our case did not have the other suggestive systemic features, such as hemifacial microsomia, vertebral column defects, choanal atresia and hypoplastic semicircular canals. We therefore posit that the phenotype described in this child was the result of the teratogenic effect of MMF.

Secondly, the duration of exposure was only 4 days and the cumulative dose was only 4,000 mg. The minimum exposure period in the previously reported cases was 8 weeks [Perez-Aytes et al., 2008]. Maternal MMF exposure in our case was approximately 7 weeks of pregnancy, during which time the external ear develops and fusion of the optic fissure occurs [Moller, 2005]. Insult from MMF during this period could result in the clinical features of microtia and coloboma, as seen in our case. We are unable to fully explain why the coloboma was unilateral. It is possible that the optic fissure fused earlier in the left eye compared to the right, and was possibly complete prior to maternal exposure to MMF. Similarly, the absence of cleft lip may be due to the completion of fusion of the maxillary prominences with the medial nasal prominences (usually also occurring around this period) before MMF exposure [Cohen, 2002].

It is interesting that in our case, the mother suffered a spontaneous miscarriage during her first pregnancy. Data from the United States National Transplantation Pregnancy Registry found that from 26 pregnancies in 18 female kidney recipients exposed to MMF, 11 (42.3%) resulted in spontaneous abortions [Sifontis et al., 2006]. However, as spontaneous miscarriage during the first 7 weeks of pregnancy is relatively common, we cannot attribute this event to the MMF exposure during the first 5 weeks of pregnancy. In addition, pathologic examination was not performed on the aborted fetus, and thus it was not determined whether the fetus had any abnormalities. The MMF dosage at that time was 500 mg three times daily, giving a cumulative dose of 52,500 mg. With a plasma half life of 16 hours, it is likely that virtually all of the MMF would have been excreted by the time of the second conception approximately 6 weeks after her initial miscarriage. It is possible that for this mother, a total MMF dose of 52,500 mg resulted in spontaneous miscarriage, while a total dose of 4,000 mg resulted in the microtia and coloboma. It may also be possible that had the MMF exposure been longer with a greater cumulative dose, the newborn would have presented with more anomalies.

Our case report lends further credence to the growing evidence of MMF-related teratogenicity. Our report also suggests that the effect on the fetus may be dependent on the dose, timing, and duration of MMF exposure. It is possible that in some individuals, a teratogenic effect is seen with a relatively small dose of MMF, particularly when exposure occurs at a critical period of development. At present, despite these reports, there is no available prospective epidemiological data that would allow an estimation of the risk of having an affected child to be made. In October 2007, the manufacturer and the United States Food and Drug Administration (FDA) disseminated information to healthcare providers regarding the increased risk of first trimester pregnancy loss and congenital malformations with maternal use of MMF during pregnancy. In addition, the pregnancy category for MMF was altered to Category D (positive evidence of fetal risk) from Category C (risk of fetal harm cannot be ruled out). The manufacturer also recommends that MMF should not be started before a negative pregnancy test has been obtained, and that effective contraception should be started before MMF treatment and be continued for at least 6 weeks after MMF is stopped. We concur fully with the recommendation that women on MMF should be fully counseled about the teratogenic risks and advised about contraception during the course of MMF therapy.

REFERENCES

Beck AE, Hudgins L, Hoyme HE. 2005. Autosomal dominant microtia and ocular coloboma: New syndrome or an extension of the oculo-auriculo-vertebral spectrum? Am J Med Genet Part A 134A:359–362.

Bullingham RE, Nicholls AJ, Kamm BR. 1998. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharkacokinet 34: 429–455.

Cohen MM Jr. 2002. Malformations of the craniofacial region: Evolutionary, embryonic, genetic, and clinical perspectives. Am J Med Genet 115:245–268.

Davis MDP, Rogers RS III, Pittelkow MR. 2002. Recurrent erythema multiforme/Stevens-Johnson syndrome: Response to mycophenolate mofetil. Arch Dermatol 138:1547–1550.

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

Moller HU. 2005. Milestones and normative data. In: Taylor D, Hoyt CS, editors. Pediatric ophthalmology and strabismus,

3rd edition. Philadelphia: Elsevier Saunders, Blackwell Science. p 32–42.

Perez-Aytes A, Ledo A, Boso V, Saenz P, Roma E, Poveda JL, Vento M. 2008. In utero exposure to mycophenolate mofetil: A characteristic phenotype? Am J Med Genet Part A 141A:1–7.

Pergola 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.

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 transplant recipients with exposure to mycophenolate mofetil or sirolimus. Transplantation 82:1698–1702.

Stromland K, Miller M, Sjogreen L, Johansson M, Joelsson BM, Billstedt E, Gillberg C, Danielsson S, Jacobsson C, Andersson-Norinder J, Granstrom G. 2007. Oculo-auriculo-vertebral spectrum: Associated anomalies, functional deficits and possible developmental risk factors. Am J Med Genet Part A 143A:1317–1325.

Tasse C, Bohringer S, Fischer S, Ludecke HJ, Albrecht B, Horn D, Janecke A, Kling R, Konig R, Lorenz B, Majewski F, Maeyens E, Meinecke P, Mitulla B, Mohr C, Preischl M, Umstadt H, Kohlhase J, Gillessen-Kaesbach G, Wieczorek D. 2005. Oculo-auriculo-vertebral spectrum (OAVS): Clinical evaluation and severity scoring of 53 patients and proposal for a new classification. Eur J Med Genet 48:397–411.

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

Velinov M, Zellers N. 2008. The fetal mycophenolate mofetil syndrome. Clin Dysmorphol 17:77–78.