



A Newborn with Pulmonary Atresia and Antenatal Colchicine Exposure

Fırat Ergin¹, Demet Terek¹, Mehmet Yalaz¹, Ertürk Levent², Özge Altun Köroğlu¹, Sibel Gökseç, Mete Akısü¹, Ferda Özkinay⁴ and Nilgün Kültürsay^{1*}

¹Department of Pediatrics, Division of Neonatology, Ege University, Turkey

²Department of Pediatrics, Division of Cardiology, Ege University, Turkey

³Department of Pharmacology, Ege University, Turkey

⁴Department of Pediatrics, Division of Genetics, Ege University, Turkey

Abstract

Colchicine treatment improved female fertility and the outcome of pregnancy in Familial Mediterranean Fever patients by preventing the serosal adhesions and controlling the acute attacks. Limited number of human series does not show any proof for increased abortus, stillbirth or teratogenic effect of colchicine. Here we present a term newborn with pulmonary atresia whose mother was on colchicine during pregnancy. These two events may be coincidentally related; however, there may be a causal relationship that has not been reported in the literature yet. Fetal echocardiography is strongly recommended for women who are pregnant and taking colchicine.

Keywords: Colchicine; Teratogen; Newborn; Heart defect; Pulmonary atresia

Introduction

Colchicine treatment improved female fertility and the outcome of pregnancy in Familial Mediterranean Fever patients by preventing the serosal adhesions and controlling the acute attacks. Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder, characterized by acute attacks of fever and serosal inflammation which is more frequent in Jewish, Armenian, Turkish and Arabic populations [1]. Untreated or inadequately treated patients have the risk of amyloidosis, which is an important cause of morbidity and mortality. Colchicine has been used in the treatment of FMF since the 1970s and remains unrivalled in this respect [2].

It is necessary to control FMF attacks during pregnancy, because peritonitis may lead to early contractions of the uterus and eventual abortions [3]. However, colchicine treatment improved female fertility and the outcome of pregnancy by preventing the serosal adhesions and controlling the acute attacks. Limited number of human series does not show any proof for increased abortus, stillbirth, or teratogenic effect of colchicine. Therefore, the present opinion is that female patients with FMF should continue taking the optimal dose of colchicine during their pregnancy and that there is no need for amniocentesis during pregnancy [1,4]. Here we present a term newborn with pulmonary atresia that may be a teratogenic effect of antenatal colchicine exposure.

Case Presentation

A 4110 gram, male infant with gestational age of 38 weeks, was delivered via cesarean section from 31-year-old primiparous mother with FMF. The mother was on 1.5 mg/day colchicine treatment. The infant's Apgar scores were 9 and 10. Infant was in normal appearance and acyanotic. His pulse oximetry oxygen saturation levels were around 90% at preductal and 88% at postductal sites. A systolic ejection murmur was heard. He was admitted to neonatal intensive care unit due to antenatal diagnosis of pulmonary stenosis (PS) on fetal echocardiography performed at 24th gestational week. Postnatal echocardiography revealed pulmonary atresia (PA) with no flow at pulmonary valve, right ventricle was hypertrophic with a second-degree tricuspid insufficiency (Figure 1). Pulmonary artery was filled via ductus arteriosus with a left to right shunt. Left ventricle and left atrium size were normal. Immediate prostaglandin infusion was initiated and urgent thorax computed tomography angiogram confirmed an atretic pulmonary valve and atrial septal defect (Figure 2).

The initial complete blood count, biochemistry and acute phase reactant studies were normal.

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*Correspondence:

Nilgün Kültürsay, Ege University Children Hospital, Head and Division of Neonatology, 35100, Bornova, Izmir, Turkey, Tel: +90 5326082890; E-mail: nilgunkultursay@gmail.com

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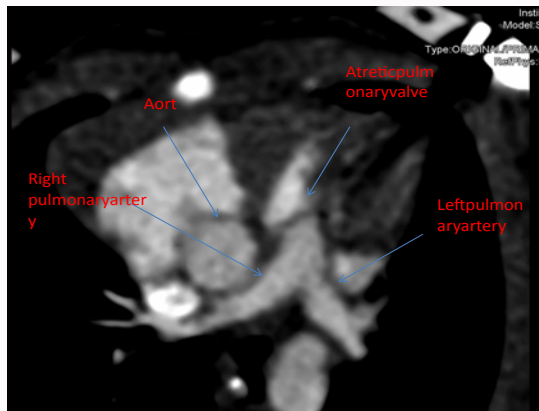


Figure 1: Thorax computed tomography angiogram axial reconstruction finding.

The infant was operated on his third day of life. Since the pulmonary valve was nearly totally atretic valvulotomy, valvuloplasty could not be performed and a modified Blalock Taussig shunt was performed.

Some epileptiform movements were seen on the sixth day of life and Levetiracetam therapy was started. Neurological examination, Electroencephalography (EEG), and cranial Magnetic Resonance Imaging (MRI) were performed. Low and immature activity for his post-conceptual age was reported in EEG. MRI revealed a hyperintense region at both parietal white matter which may be due to hypoxia related to his severe cardiac defect. As etiologic investigation of cardiac defect, infant's TORCH serology and FISH analysis for Di George Syndrome and karyogram analysis resulted normal.

Discussion

We here report a newborn infant with isolated severe valvular PA born to a mother with FMF treated with colchicine throughout her pregnancy.

Pulmonary stenosis is a common congenital heart defect, characterized by flow obstruction from right ventricle to pulmonary arteries. It occurs in 0.6 to 0.8 per 1000 live births either isolated or associated with some genetic syndromes [5]. It may also develop due to some perinatal infections. PS may be a component of the syndromes such as Noonan syndrome, Alagille syndrome, Williams-Beuren syndrome and Congenital rubella syndrome [1,5]. So far, the relationship between FMF, colchicine treatment and PA have not been reported.

In cases with critical PA, the severity of the right ventricular outflow tract (RVOT) obstruction is life-threatening, because of inadequate antegrade pulmonary blood flow and survival is dependent on maintaining patency of the ductus arteriosus by the administration of prostaglandin E1 (alprostadil) therapy. Our patient had a severe PA which was diagnosed antenatally and urgently treated with prostaglandin infusion followed by an MBT shunt diverting some systemic flow to pulmonary arteries.

Increased infertility is seen, particularly in untreated women with FMF, as a result of ovulatory insufficiency and peritoneal adhesions (because of attacks or operations). At present, the gold standard treatment for FMF is colchicine. The incidence of spontaneous abortions before colchicine treatment is around 25–30% [2]. Development of peritoneal adhesions can be decreased and fertility can be achieved, with colchicine treatment. Some studies have

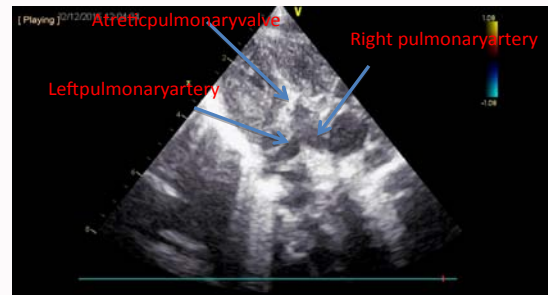


Figure 2: Echocardiography finding.

reported that premature births and spontaneous abortions are also increased in patients treated with colchicine [6].

There are some concerns about colchicine use in perinatal period. Colchicine acts on the microtubular structure of cells and may affect various cellular processes such as mitosis. Laboratory studies have reported that chromosome aberrations due to the negative effect of colchicine on mitosis [7]. Animal data shows that colchicine and its derivative demecolcicine is teratogenic in mice and rabbits in low doses and embryocidal in mice, rats and rabbits in higher doses [8]. However, animal studies with colchicine did not result in any chromosome aberrations. No congenital malformations were reported in a small number of human fetuses exposed to colchicine [9].

Colchicine may cause morphological abnormalities by induction of vascular epithelial cell apoptosis via JNK activation [10]. Antenatal colchicine exposure may be related to structural malformation in a similar way. Cancer studies in adults also shows antivascular effects by disruption of cytoskeletal structure [11].

Colchicine is in category C in FDA Reports and in category D in New Zealand and Australia Reports. Demonstration of the passage of colchicine through the placenta and case reports of trisomy in the children of women using colchicine have caused serious concerns. Analysis of large-scale monitoring data showed that no difference in cytogenetic abnormalities was observed in patients taking colchicine during pregnancy compared with those not taking colchicine [12]. The reported cases with trisomy 21 is thought to be coincidental.

Therefore, cessation of colchicine should not be recommended in conception and throughout pregnancy even in patients with symptomatic remission. As amniocentesis is an invasive procedure with a risk of miscarriage and infection, some investigators have questioned the need for this procedure and reported that amniocentesis was not required in patients taking colchicine during pregnancy [13].

Colchicine may be excreted into breast milk. Studies have reported that the drug reached the maximum level in breast milk 1-2 hours after administration. On the other hand, when the amount passed to the child was analyzed, it was observed to be only one-tenth of the maternal dose [14]. Therefore colchicine is safe in breast feeding mother, but mothers are recommended not to breastfeed within 0.5-2 hours of oral drug intake which is the peak time for serum drug levels.

In our case, maternal colchicine treatment and severe PS and some hypoxic brain manifestations which are probably due to the severity of PS in the offspring, may be coincidentally related; but it may also show a rare causal relationship that was not reported in

literature so far. Fetal echocardiography is strongly recommended for women who are pregnant and taking colchicine.

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