

Fetal Warfarin Syndrome

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Fetal warfarin syndrome (FWS) or warfarin (coumadin) embryopathy is a rare condition as a result of fetal exposure to maternal ingestion of warfarin during pregnancy. A male infant, whose mother was treated with the anticoagulant (warfarin) because of a mechanical heart valve replacement after rheumatic heart disease, presented with signs of warfarin embryopathy. The facial dysmorphism included hypoplasia of nasal bridge, laryngomalacia, pectus carinatum, congenital heart defects (atrial septal defect and patent ductus arteriosus), ventriculomegaly, stippled epiphyses, telebrachydactyly, and growth retardation. The pathogenesis and management of FWS are discussed. (*Chang Gung Med J* 2004;27:691-5)

Key words: fetal warfarin syndrome, anticoagulant, embryopathy.

Anticoagulant therapy during pregnancy is indicated for the treatment and prophylaxis of venous thrombo-embolic disease and systemic embolism associated with valvular heart disease and/or prosthetic heart valves.⁽¹⁾ However, this is problematic because both heparin and warfarin can potentially produce adverse effects in mothers and fetuses.⁽²⁾ Warfarin sodium is a low molecular weight anticoagulant that readily crosses the placenta and may cause spontaneous abortion, stillbirth, neonatal death, and a variety of congenital anomalies known as fetal warfarin syndrome (FWS).^(1,2) The teratogenic effects may occur from exposure during either the embryonic period or the fetal period. The pathogenesis is probably from hemorrhages into any of several organs secondary to vitamin K deficiency induced by warfarin.⁽³⁾ A woman with rheumatic heart disease underwent a mechanical valve replacement, followed by life-long anticoagulant (warfarin) prophylaxis. She had two pregnancies with two different outcomes. I present the findings of her child with FWS.

CASE REPORT

A male infant was born via cesarean section at

26 weeks of gestation to a 37-year-old, gravida 2, para 2, woman. There was no history of consanguinity. The mother had suffered from rheumatic heart disease complicated with mitral valve regurgitation and stenosis, and severe tricuspid valve regurgitation for several years. She underwent mitral valve replacement with St. Jude-Mech valve and tricuspid annuloplasty at the age of 32 years due to the cardiac status being functional class III (according to the American Heart Association). Since then she has taken warfarin sodium (coumadin) as an anticoagulation prophylaxis at an average daily dosage of 5 mg. The prothrombin time was regularly followed up and kept at around 30-35 seconds. Warfarin was given throughout her two pregnancies. Her first baby was a male born at term with a birth body weight (BW) of 2200 g and body length (BL) of 47 cm. The postnatal health and growth were good without facial dysmorphism, except for right cryptochidism and mild pigeon chest.

However, her second pregnancy course was complicated with polyhydramnios and premature rupture of the membrane. Tocolytic agents were given and the warfarin was changed to heparin at 22nd week of gestation, but it was not effective.

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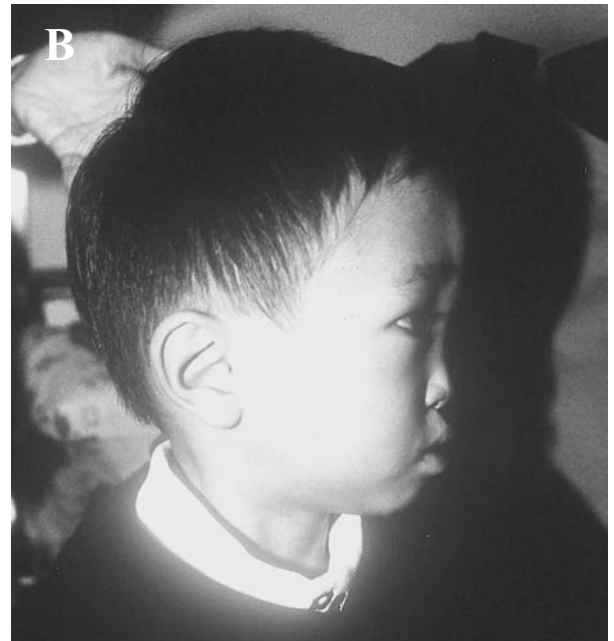
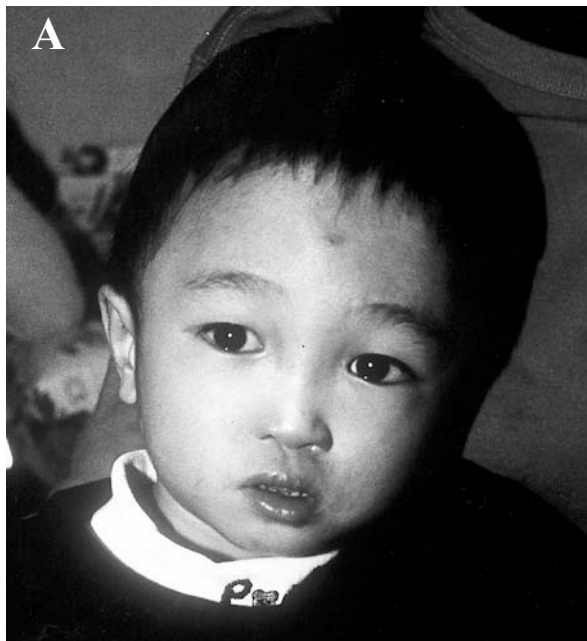
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After delivery of the infant at 26 weeks of gestation, the mother was complicated with internal bleeding, and the infant was in severe respiratory distress with Apgar scores of 3 and 5 at 1 minute and 5 minutes, respectively. Physical examination results showed his BW was 675 g, BL was 33.0 cm, and head circumference (HC) was 22.0 cm. Facial dysmorphism was noted including nasal hypoplasia, a depressed nasal bridge with a deep groove between the alae nasi and nasal tip, and a small nose on the facial profile view (Figs. 1). Noisy breathing sounds were mentioned and laryngomalacia with tracheomalacia was detected using fibro-optic bronchoscopy. In addition, short neck, pectus carinatum, and telebrachydactyly were found. Congenital heart defects (CHD), i.e. atrial septal defect and patent ductus arteriosus, were detected using echocardiography at 7 days of age, which disappeared at the age of 2 months and 2.5 years, respectively. Brain ultrasonography showed ventriculomegaly. X-ray studies showed relatively short femurs and stippling of the lower vertebrae and the uncalcified epiphyses of the calcanei, which is compatible with chondrodysplasia punctata (Fig. 2). During the first 2 years of life, the infant was complicated with neonatal necrotizing enteritis, anemia, retinopathy of prematurity, and

chronic lung disease. His growth was markedly retarded, with BW, BL and HC all below the 3rd percentile at the age of 3 years. His fingernails were hypoplastic. The threshold to pain and itching sensation were also found to be decreased. Bilateral



Fig. 2 X-ray at 1 day of age shows stippling in the sacral area and tarsal bones (arrow).



Figs. 1 (A) The patient at age 3 years. (B) Hypoplasia of the midface and nose.⁽⁸⁾

peripheral auditory conduction by brainstem auditory evoked potential test and osteopenia (-2.54 SD for his age) by bone mineral densitometry were detected. No history of seizure was noted. The spine films showed mild scoliosis and the stippling disappeared.

DISCUSSION

I presented a case of warfarin embryopathy or FWS. The diagnosis is based on the history of maternal ingestion of vitamin K-antagonist anticoagulant in therapeutic doses during the first two trimesters of pregnancy in association with threatened abortion, and typical facial malformations (hypoplastic nose), and stippled epiphyses.

Warfarin sodium or coumadin is an anticoagulant that depresses synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and is used in the treatment of a variety of thrombo-embolic disorders and in those at significant risk of thrombus development.^(4,5) Because of its low molecular weight, warfarin easily crosses the placenta, resulting in significant levels in the fetus. Therefore, both mother and fetus receive the anticoagulant effects. A pattern of congenital anomalies (nasal hypoplasia and stippling of vertebrae or bony epiphyses) has been well recognized in more than 6% of children born to mothers treated with warfarin during the first trimester.^(1,2,5-7) Nasal hypoplasia and depression of the bridge of the nose may lead to the flattened and upturned appearance. A deep groove between the alae nasi and the tip of the nose, probably secondary to undergrown cartilage, is often present. Therefore nares and air passages may be small, leading to neonatal respiratory distress secondary to upper airway obstruction in about one-half of the patients. Stippling in unclassified epiphyseal regions occurring in the axial skeleton and the proximal femurs may not be evident after the first year of life.⁽⁷⁾ In about half of the subjects reported, variable degrees of hypoplasia of the extremities were found, ranging from severe rhizomelia to dystrophic nails and shortened fingers.^(1,7) Timing of exposure appears to be a critical factor for those with FWS.^(1,7) Infants exposed to vitamin K antagonists during the second and third trimesters seem to have an increased risk of structural anomalies in the central nervous system (such as microcephaly, hydrocephalus, agenesis of corpus callosum, and Dandy-Walker malformation) as well as eye

anomalies (optic atrophy, microphthalmia, and Peter anomaly of eye).^(1,2,4,7) Blindness may be present in cases with exposure to coumadin during all three trimesters. In addition, an increased number of stillbirths, spontaneous abortions, neonatal deaths, and premature delivery occur in women taking vitamin K antagonists during the second and third trimesters.^(1,6) Furthermore, the effects of warfarin, which are difficult to reverse, are seen for a considerable period of time after the administration is discontinued.^(1,7) Thus, if taken until the child is delivered, excessive bleeding in both mother and child may occur.⁽⁸⁾ Other clinical findings of FWS include scoliosis (17%), significant development retardation (31%), deafness (12%), CHD (8%), and seizure (4%).⁽⁷⁾ Overall, one half of the subjects apparently had no severe disability. All patients with developmental retardation, blindness, and deafness were those exposed to coumadin during all three trimesters.

The process of osteocalcin carboxylation in human bone formation is a vitamin K-dependent process and that circulating osteocalcin will be altered structurally by warfarin administration.⁽⁹⁾ This finding has pathophysiological implications for the fetal warfarin embryopathy syndrome, bone disease associated with chronic liver diseases, and possibly for osteoporosis, in which vitamin K deficiency has been implicated.⁽¹⁾ The similarity between FWS and X-linked recessive chondroplasia punctata (CPDX) has suggested a common pathogenesis for these two disorders. Warfarin appears to inhibit arylsulfatase, a genetically determined deficiency which is responsible for CPDX.^(3,10)

Women with mechanical prosthetic heart valves should be counseled before conception about the risks of anticoagulant therapy during pregnancy. Therapy for pregnant women with prosthetic heart valves is problematic because warfarin is fetopathic and the efficacy of heparin has not been established.⁽⁴⁾ For the prophylaxis and treatment of venous thrombo-embolic disease in pregnant patients, heparin is the preferred anticoagulant because its efficiency and safety have been established.⁽⁴⁾ However, because the efficacy of heparin in preventing systemic embolisms in patients with prosthetic heart valves has not been established, either adjusted-dose heparin or a combination of heparin and oral anticoagulants can be used.⁽¹⁾ Recently, a comparison for the tolerability and safety of three fixed doses of

ximelagatran versus warfarin in patients with nonvalvular atrial fibrillation was performed. Ximelagatran is a novel, oral direct thrombin inhibitor and was noted to be safe and effective,⁽¹¹⁾ and it may be administered in pregnant patients.

Not all women taking oral anticoagulants during the critical period have affected infants, as in this case family. The prognosis of FWS varies with severity of defects. Infants often present with upper airway obstruction, which can be relieved by the placement of an oral airway. Fortunately, the small nasal passages will enlarge with age. Scoliosis may develop if the vertebrae were involved with stippling. However, the stippling is incorporated into the calcified epiphyses and has resulted in few problems. Of significantly affected infants, those with hemorrhages or CNS abnormalities generally do poorly, whereas one-half of those with embryopathy have been recorded as doing very well.^(1,7,10)

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胎兒warfarin症候群

侯家瑋

胎兒 warfarin 症候群是一種極罕見的胚胎病，主要是因為胎兒長期暴露於使用 warfarin 之母體後受到傷害所致。一名男孩因母親罹患風濕性心臟病接受機械性心臟瓣膜置換後，需要服用抗凝血劑 warfarin 而罹患胎兒 warfarin 症候群，特徵包括鼻樑低下、喉頭軟化、雞胸、先天性心臟病、腦室擴大、點狀性軟骨形成不良、手指畸形及生長遲滯。本文將討論胎兒 warfarin 症候群其致病機轉及處理方式。(長庚醫誌 2004;27:691-5)

關鍵字：胎兒 warfarin 症候群，抗凝血劑，胚胎病。

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