The Journal of Laryngology and Otology
February 1986. Vol. **100.** pp. 215–219

The congenital warfarin syndrome

by

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Introduction

Warfarin, a coumarin derivative, is an oral anticoagulant which has been in clinical use for 30 years. Before its introduction as a safe anticoagulant drug, warfarin was a useful rodenticide which acted by inducing fatal haemorrhage in rats. In 1951, a man survived a suicide attempt by ingestion of a large amount of warfarin. This led to clinical trials which established the safety of its use in humans (Gilman *et al.*, 1980).

It has been known for years that warfarin treatment during the later months of pregnancy can cause foetal or placental haemorrhage, but no knowledge was originally available about the teratogenic effect of this drug. DiSaia (1966) reported the first case of congenital anomaly due to maternal warfarin treatment. Since then several cases with similar abnormalities have been recorded and the congenital warfarin syndrome has been clearly established. This syndrome consists of: nasal hypoplasia, stippling of bone, optic atrophy and mental retardation.

Other congenital malformations due to warfarin given during pregnancy were described by Cox *et al.* (1977) in a child born with a complex congenital heart defect, absent spleen, midline liver, partial failure of gut rotation and atresia of the left colon.

The purpose of this paper, in addition to reporting a rare congenital nasal deformity due to warfarin embryopathy, is to alert medical practitioners to the potential teratogenic effect of warfarin. The congenital anomalies affecting various organs and the possible mechanism of warfarin teratogenesis are also discussed.

Case Report

The mother, a 28-year-old woman, had been on warfarin for 9 years following a left hemiplegia from which she made a complete recovery. She was born with a ventricular septal defect which was successfully repaired by open heart surgery when she was 11 years old. After the birth of her first normal child at the age of 18, she used the contraceptive pill until she suffered from a cerebrovascular accident which was thought to be due to embolism from a mural thrombus in the left ventricle. The contraceptive pill was stopped and treatment with warfarin began.

Subsequently, while taking warfarin, she had two uncomplicated pregnancies giving birth to normal children.

Her fourth pregnancy ended after 38 weeks in the normal delivery (on 14 July 1984) of a male child weighing 2720 gm. The baby was cyanosed at birth but his colour improved with oxygen therapy. It was also noted that his nose was small and flat, with hypoplasia of the nasal bones (Fig. 1). No other abnormalities were detected on clinical examination. The patency of the posterior nares was confirmed by passing fine catheters through the nose. Examination of the fundi showed no evidence of optic atrophy.

Skeletal survey revealed hypoplasia of the nasal bones (Fig. 2) and stippling of the tarsal bones (Fig. 3) but no other bony abnormalities.

Despite feeding problems in the early weeks of life, the child gained weight normally and his breathing improved as he learned to breathe through his mouth.

Discussion

Congenital malformations of the nose are rare. Posterior choanal atresia is probably the commonest congenital disease of the nose. Other rare

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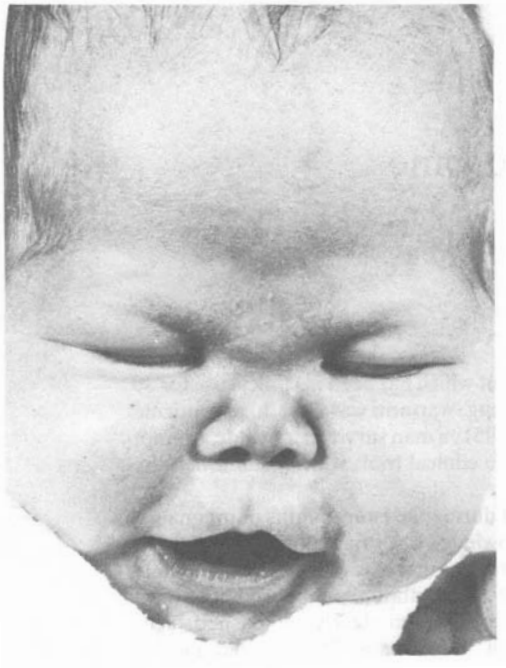


FIG. 1
Facial photograph at two weeks of age illustrating the hypoplastic nose.

congenital nasal deformities include: cleft lip, dermoid cysts and encephalocoeles. Complete or partial absence of the nose, double nose and proboscis lateralis have also been reported.

Nasal deformities are also described in the following hereditary diseases:

I. Autosomal dominant diseases

1. Waardenburg syndrome: Broad nasal bridge with prominent epicanthic folds.
2. Achondroplasia: Depressed nasal bridge with midfacial hypoplasia.
3. Apert disease: Midfacial hypoplasia and hypertelorism.

II. Autosomal recessive diseases

Mucopolysaccharidosis Type IH (Hurler syndrome): Broad nose, wide nostrils and flat bridge.

III. Diseases determined by multifactorial inheritance

Cleft lip and cleft palate.

Anticoagulants given during pregnancy carry a substantial risk both to the mother and to the foetus and they should be used only when there are definite indications for their administration. There are conditions such as thrombo-embolic disease, artificial cardiac valves and congenital heart diseases where long-term anticoagulant treatment is necessary. The usual form of treatment during pregnancy is to give warfarin until 4 weeks before the expected date of delivery, when it is replaced by heparin given subcutaneously to deplete the foetal tissues of the anticoagulant effect of warfarin and to prevent foetal and placental haemorrhage (Ikonen *et al.*, 1970).

Foetal anomalies produced by maternal warfarin therapy

Warfarin, because of its low molecular weight, crosses the placenta and if given early in pregnancy may result in the congenital warfarin syndrome. Hypoplasia of the nasal bones is the commonest anomaly reported in this syndrome. The nose is flat, the nasal septum is short and a deep groove between the ala nasi and the tip of the nose is sometimes present. True choanal stenosis is also documented (Hall *et al.*, 1980). The nasal abnormality usually results in breathing and feeding difficulties, with cyanotic attacks in the first few weeks of life until the child learns to breathe through his mouth. Frequent nasal toilet is often necessary, to clear the nasal passages, by removing the secretions and crusts.

As the affected infant grows, the nose remains relatively small but parents can be reassured that in most cases it will improve cosmetically and functionally (Shaul and Hall, 1977). Long-term observation will be required.

Bony abnormalities in the form of stippling of epiphyses, short limbs, short fingers and kyphoscoliosis are also common. The stippled epiphyses gradually disappear as they become incorporated into the growing bones. The bony deformities are similar to those found in the milder form of chondrodysplasia punctata, a hereditary disease characterized by ectopic calcification of cartilage occurring either as a severe lethal autosomal recessive form or as the milder autosomal dominant Conradi-Hunermann type (Spranger *et al.*, 1971).

Central nervous system malformations are reported frequently. They include: mental retardation, hydrocephalus, microcephaly, hypotonia and seizures. Eye deformities in the form of optic atrophy, blindness and corneal opacities are also frequent.

Anomalies affecting other organs have been reported sporadically: deafness, congenital heart

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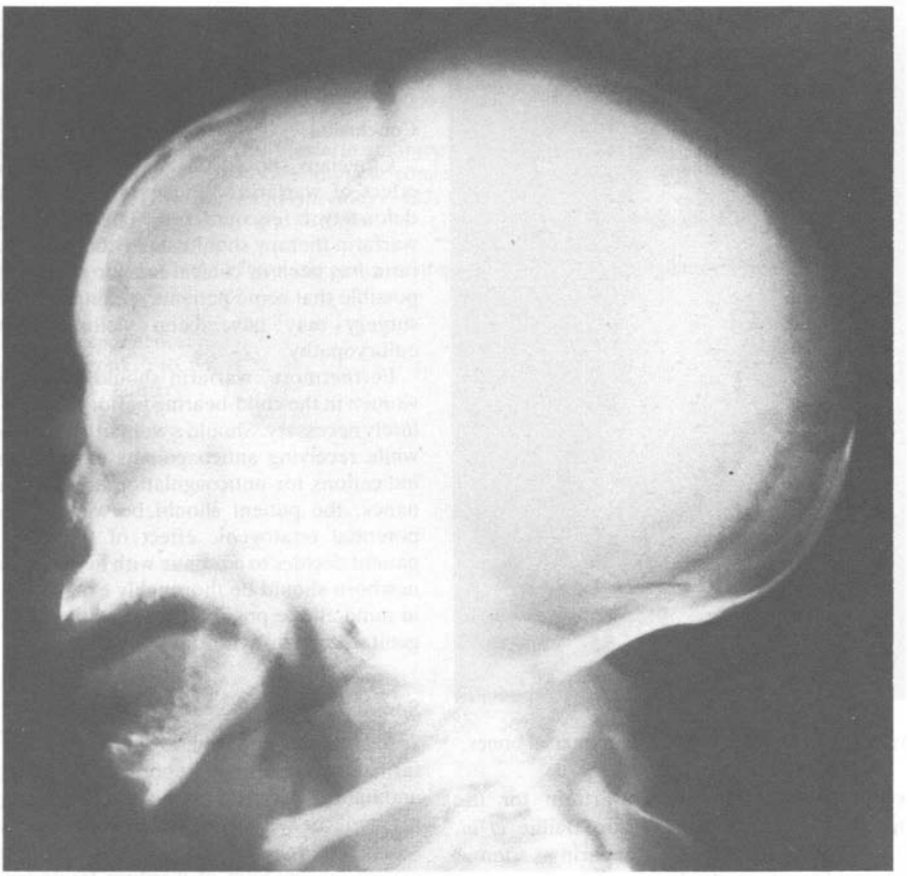


FIG. 2
Lateral X-ray of the skull revealing the hypoplastic nasal bones.

disease, absent spleen, midline liver and atresia of the left colon are among those infrequently reported (Hall *et al.*, 1980; Cox *et al.*, 1977).

Mechanism of warfarin teratogenesis

The exact mechanism of warfarin teratogenesis is uncertain. The bony deformities are believed to be due to microhaemorrhages into the foetal cartilages which heal by calcification, giving the bone a stippled appearance on X-ray examination (Becker *et al.*, 1975). The central nervous system abnormalities are due either to a direct teratogenic effect (Holzgreve *et al.*, 1976) or to haemorrhage into the foetal nervous tissue which results in fibrosis and distorted growth (Hall *et al.*, 1980).

As warfarin is a vitamin K antagonist, Shaul and Hall (1977) believe that the congenital anomalies could be manifestations of foetal vitamin K deficiency. Nasal and bony abnormalities may result if warfarin is given in the first trimester (Whitfield, 1980), while neurological and eye malformations may be produced by warfarin given in the second and third trimesters (Hall, 1976).

Warfarin or heparin?

Pauli and Hall (1979) analysed all published cases in which coumarin derivatives were administered during pregnancy. They found that about 1 in 6 of such pregnancies resulted in liveborn infants with warfarin embryopathy, about 1 in 6 in stillbirths or spontaneous abortions and only two-thirds resulted in apparently normal liveborn infants.

Heparin, because of its large molecular weight, does not cross the placenta and would seem to have

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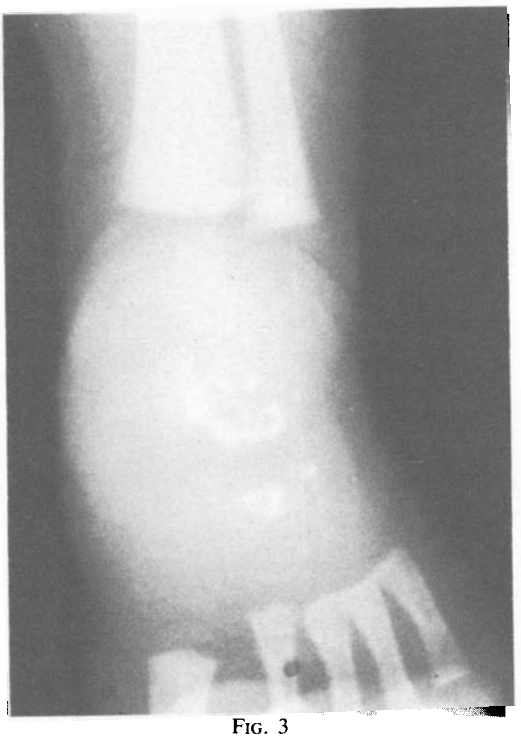


FIG. 3
X-ray of the foot showing the stippled tarsal bones.

a theoretical advantage over warfarin for use during pregnancy. For this reason Baillie *et al.* (1980) change to subcutaneous heparin as soon as pregnancy is reported. In practice, however, heparin during gestation does not result in a significantly better outcome. Hall *et al.* (1980) reviewed 135 cases where heparin was used and found that the infants in one-eighth were stillborn, in one-fifth premature (a third of whom died) and in two-thirds apparently normal.

It is clear that both heparin and warfarin are equally dangerous during pregnancy. Neither drug is superior to the other and more information is needed on which to base a rational policy of anticoagulation in pregnancy.

Conclusion

Clinicians should be aware of the teratogenic effect of warfarin. Whenever a congenital nasal deformity is encountered a history of maternal warfarin therapy should always be sought. As warfarin has been in clinical use for a long time, it is possible that some patients seeking cosmetic nasal surgery may have been victims of warfarin embryopathy.

Furthermore, warfarin should not be given to women in the child-bearing period unless it is absolutely necessary. Should a woman become pregnant while receiving anticoagulants or should medical indications for anticoagulation arise during pregnancy, the patient should be warned about the potential teratogenic effect of the drug. If the patient decides to continue with her pregnancy, the newborn should be thoroughly examined, bearing in mind all the possible manifestations of the congenital warfarin syndrome.

Summary

A rare congenital nasal deformity due to warfarin embryopathy is reported. The commonest anomalies described in this syndrome are: hypoplasia of the nose, stippling of bone, optic atrophy and mental retardation. The various abnormalities and the mechanism of warfarin teratogenesis are discussed.

Acknowledgement

I would like to thank Mr. G. Buchanan, for his advice and encouragement; Dr. H. Leibeschuetz, for allowing me to report his case; and the Photographic Department at Southend Hospital, for the illustrations.

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