Brief Clinical Report

Severe Cervical Dysplasia and Nasal Cartilage Calcification Following Prenatal Warfarin Exposure

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We present an infant who was exposed to warfarin throughout pregnancy and has warfarin embryopathy. When the child was examined radiologically at 20 months areas of calcification were visible in the septal and alar cartilages of the small external part of the nose. The location of this ectopic calcification is consistent with that seen in an animal model of the warfarin embryopathy. It supports the hypothesis that warfarin interferes with the prenatal growth of the cartilaginous nasal septum by inhibiting the normal formation of a vitamin K-dependent protein that prevents calcification of cartilage. The child also had severe abnormalities of the cervical vertebrae and secondary damage to the spinal cord. Cervical vertebral anomalies are a relatively common finding in the warfarin embryopathy and in the related Binder syndrome. Am. J. Med. Genet. 71:391–396, 1997.
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KEY WORDS: warfarin embryopathy; ectopic calcification; stippling; vitamin K deficiency; Binder syndrome; chondrodysplasia punctata

INTRODUCTION

Exposure to warfarin during the first trimester of pregnancy, particularly in weeks 6 to 9, may be asso-ciated with a syndrome of nasal hypoplasia, depressed nasal bridge, stippled epiphyses, and distal digital hypoplasia [Hall et al., 1980]. If warfarin is replaced with heparin during weeks 6–12 of development there is evidence that the embryopathy does not occur [Iturbe-Alessio et al., 1986].

The main biochemical property of warfarin is the prevention of vitamin K recycling [Suttie, 1991]. Regular administration of warfarin rapidly causes vitamin K deficiency and vitamin K-dependent proteins, such as prothrombin, are produced in a non-functional form. Since warfarin readily crosses the placenta, it can also affect vitamin K recycling in the embryo. The result is reduced availability of vitamin K for transfer to the embryo and inhibition of recycling in the embryo. Hence, when a pregnant woman is given warfarin it is likely that the embryo will become severely vitamin K deficient. During the first trimester, this has no effect on blood clotting ability in the embryo as vitamin K-dependent clotting factors are essentially absent at this stage [Holmberg et al., 1974]. However, there are at least two other vitamin K-dependent proteins that are thought to be present in the first trimester embryo-matrix gla protein (MGP) in cartilage, bone, and other tissues [Otawara and Price, 1986] and bone gla protein (BGP) in bone [Price et al., 1981]. It has been suggested that interference with the formation of one or both of these proteins is the cause of the warfarin embryopathy.

Studies in rats have shown that warfarin exposure during early development of the midface results in reduced longitudinal growth of the nasal septal cartilage; this gives the rats a snub-nosed appearance comparable with the nasal hypoplasia of the warfarin embryopathy [Howe and Webster, 1992]. Histological examination of the nasal septum from warfarin-treated rats demonstrated large areas of ectopic calcification in the septal cartilage. This led to the suggestion that warfarin interferes with the development and growth of cartilage by inhibiting the normal formation of MGP: a vitamin K-dependent constituent of cartilage. There is

some evidence that a normal function of MGP is the inhibition of calcification in cartilage [Price et al., 1982].

The infant we present here was exposed to warfarin throughout pregnancy and has the facial changes of the warfarin embryopathy. When examined radiologically at 20 months, areas of calcification were clearly visible in the septal and alar cartilages of the small external nose, consistent with the animal studies. The child also has severe abnormalities of the cervical vertebrae and secondary damage to the spinal cord.

CLINICAL REPORT

The patient is the first child of an 18-year-old women who had antithrombin III deficiency diagnosed at age 17 following a pulmonary embolus. Her father, age 59, has antithrombin III deficiency, a diagnosis made 5 years earlier following recurrent thrombi; in retrospect, his mother probably was affected.

The 18-year-old women had been treated with warfarin since the diagnosis of antithrombin III deficiency and was maintained on warfarin throughout the pregnancy. Initially the dose was 11 mg per day reduced to 6 mg per day during mid gestation. Warfarin was suspended 2 weeks before delivery and labour was induced at 40 weeks gestation. The child was born vaginally with a birth weight of 2,420 g. He developed respiratory distress soon after birth and required oxygen.

The child was transferred to the Children's Hospital in Sydney on day 2. On examination, the child was intubated through the mouth and was in no distress. He had maxillary hypoplasia with severe hypoplasia of the nose and of the distal parts of the digits-fingers and toes (small nails and tapering fingers). A skeletal survey showed stippling in the ankles, hips, proximal humerus and vertebral column (Figs. 1, 2). There was hypoplasia of the vertebral bodies in the cervical region and loss of normal cervical lordosis. Ultrasound study of the head suggested ischemic changes in the basal ganglia and calcification of the nasal septum. Ophthalmological assessment and results of hearing screen were normal. When extubated, the child had mild upper airways obstruction probably due to nasal obstruction that settled over the next few days.

At 2 months head ultrasound findings were normal. There was development of a left ptosis and motor deficit over the next 12 months, which was initially thought to be due to cerebral palsy but subsequently it was clear that there was a cervical cord lesion and Horner syndrome associated with severe kyphosis of the cervical spine. A diagnosis of anti-thrombin III deficiency was confirmed.

At the age of 20 months the child still had maxillary hypoplasia with a small nose and distinct alar cartilages (Fig. 3). Radiographs taken at this time confirmed calcification in the nasal septum and alar cartilages (Fig. 4). There was also residual epiphyseal stippling in the wrists, proximal humerus, elbows and distal ends of the tibia, and hypoplasia of the distal phalanges of the fingers. The upper limbs were held with the shoulders abducted and with 60° flexion contractures of the elbows. There was generalized hypotonia with marked head lag. Voluntary movement was confined to the muscles innervated by the cranial nerves and to the shoulder girdle. Sensory findings were unreliable. Deep tendon reflexes were decreased in the upper limbs and exaggerated in the lower limbs. By 20 months, the patient was clearly quadriplegic. This condition was associated with severe angular kyphosis of the cervical part of the vertebral column centered at the fourth cervical vertebra (Fig. 5) with softening and secondary syringomyelia of the cervical spinal cord (Figs. 6, 7). MRI scans revealed the brain to be normal, although neonatal ultrasound study had suggested ischaemic changes in the basal ganglia.

DISCUSSION

The presence of calcified areas in the nasal septum and alar cartilages of the external nose of this infant is exactly the pathology predicted from the rat model of the warfarin embryopathy. Warfarin causes abnormal calcification of cartilage and decreased growth of the cartilage; how these two changes are interdependent is unknown. Normal prenatal development of the nose and midface is thought to depend on prolonged longitudinal growth of the nasal septum [Scott, 1953]. Interference with this growth would result in various degrees of nasal and midface hypoplasia. The size of the external nose depends on the extent that the nasal septum protrudes beyond the maxillae. Normally only about 20% of the longitudinal length of the septum extends beyond the bony boundary of the face, so even a small reduction in the length of the septum has a dramatic effect on the size of the external nose, i.e., a 10% reduction in the length of the septum could cause a 50% reduction in protrusion of the nose [Howe and Webster, 1992].

Ectopic punctate calcification (stippling) is seen regularly in warfarin embryopathy, most commonly in the epiphyses of the axial skeleton (vertebrae and pelvis), proximal femora, and calcanei [Hall et al., 1980]. However, it can potentially occur in any cartilaginous area and in published warfarin cases stippling has been observed in the epiphyses of all of the long bones, scapulae, distal phalanges of the hand, tarsal bones, distal phalanges of the feet, cartilages of the ribs, and the laryngeal/tracheal cartilages [Pauli et al., 1976; Abbott et al., 1977; Robinson et al., 1978]. Premature calcification of the hyoid bone has also been described [Becker et al., 1975]. There has been only one previous case report in which stippling around the nasal area has been reported [Shaul et al., 1975], although Shaul and Hall [1977] implied they had seen nasal stippling in more than one case. The lack of reports of nasal stippling is probably due to difficulty in examining the nasal septum/alar cartilages in standard lateral X-ray films due to the nasal hypoplasia. Interestingly, ectopic calcification is not only seen after prenatal warfarin exposure but can also occur after prolonged warfarin treatment in the postnatal period resulting in ectopic calcification in the growing cartilages of the trachea and larynx [Rifkin and Pritzker, 1984; Taybi and Capi-
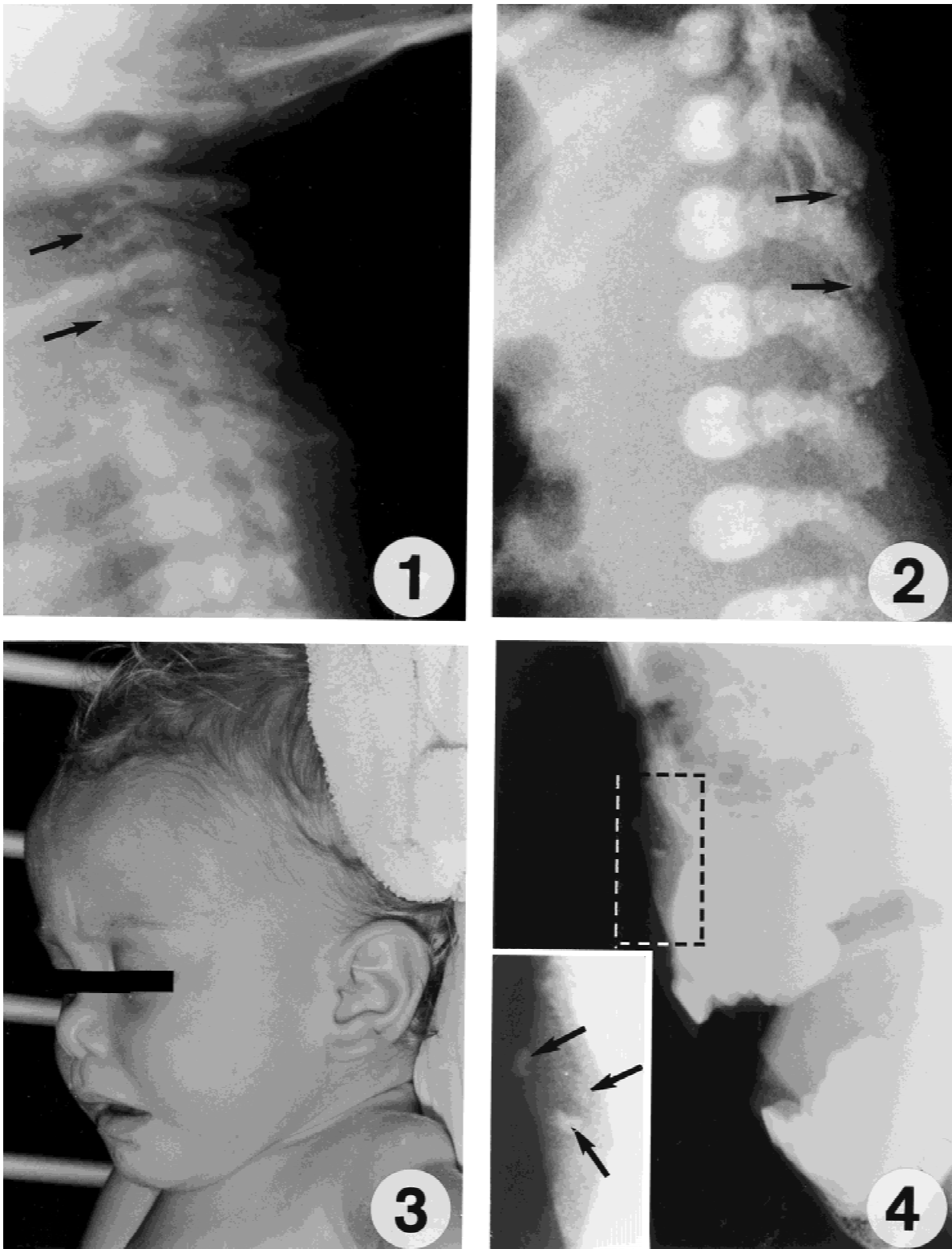
Fig. 1.   Lateral cervical radiograph at 2 days of age. There is extensive stippling (arrows) in the bodies of the upper cervical vertebrae.

Fig. 2.   Lateral thoracolumbar radiograph at 2 days of age. Extensive stippling in the posterior arches of the lumbar region.

Fig. 3.   Lateral view of patient at age 20 months. Note severely depressed nasal bridge and hypoplastic alar cartilages.

Fig. 4.   Lateral radiograph of patient at 20 months. The inset shows an enlargement of the nasal area with three distinct areas of calcification (arrows). The most distal of these areas is in the end of the nasal septum. The other two may be in the alar or septal cartilages.
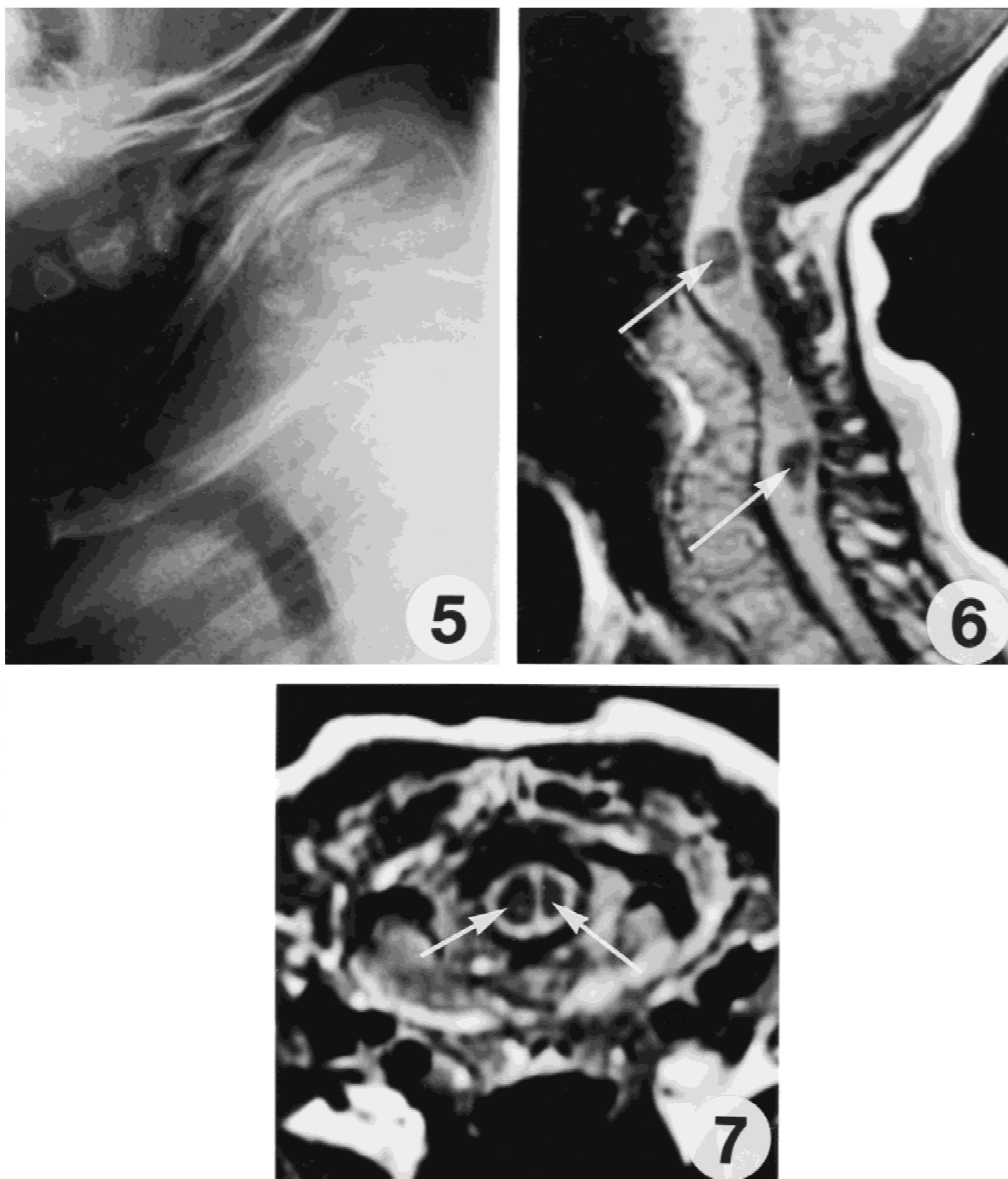
Fig. 5.   Lateral radiograph of patient at 20 months. There is marked angular kyphosis centered at the fourth cervical vertebra.

Fig. 6.   Sagittal CT scan through the upper vertebral column taken at 20 months of age. There are two large cavities (arrows) in the upper and lower cervical spinal cord.

Fig. 7.   Transverse CT scan through upper cervical cord showing two cavities (arrows) in the spinal cord.

tanio, 1990]; to date effects on the nasal septal carti-lage have not been reported.

The severe neurological deficits seen in this case are almost certainly due to the abnormalities of the upper cervical vertebrae. The severe angular kyphosis of the cervical part of the vertebral column has led to com-pression of the cord with subsequent development of syringomyelia. Abnormalities in the cervical curvature

were evident at 2 days of age and were associated with widespread stippling and hypoplasia of the vertebral column.

Severe vertebral anomalies have occasionally been reported in warfarin embryopathy [Baillie et al., 1980; Harrod and Sherrod, 1981; Hosenfeld and Wiedemann, 1989; Shaul and Hall, 1977], accounting for 25% of cases in one followed-up series [Hall et al., 1980]. In

some cases the vertebral anomalies have led to scoliosis [DiSaia, 1966; Gooch et al., 1978; Hall et al., 1980; Hosenfeld and Wiedemann, 1989]. One child who died at age 10 had scoliosis, posterior wedging of vertebrae, odontoid dysplasia, and subluxation of C1 on C2 [Gooch et al., 1978]. Thoracic butterfly vertebrae [Harrod and Sherrod, 1981] and cranial to caudal tapering of lower thoracic to lumbar vertebral bodies have also been reported [Hosenfeld and Wiedemann, 1989].

Warfarin-affected children seen by orthodontists or plastic surgeons are often diagnosed as Binder syndrome. Binder syndrome is characterised by the same midfacial hypoplasia seen in the warfarin embryopathy and when radiographs are available from the neonatal period these usually demonstrate stippling. Binder syndrome is heterogenous and besides warfarin cases it also includes genetic and other environmental causes [Howe et al., 1992]. Studies of these patients show that between 25 and 50% have abnormal cervical vertebrae [Horswell et al., 1988; Resche et al., 1980; Olow-Nordenram, 1987]. Common abnormalities include spurs, a hypoplastic odontoid, kyphosis, persistent chorda dorsalis, short posterior arch of C1, and occipitalization.

Similarly cases of genetic chondrodysplasia punctata (CP) (also sometimes designated Binder syndrome because of their midface hypoplasia) frequently have vertebral anomalies. Children with rhizomelic CP have the common radiological finding of coronal clefts of lumbar and thoracic vertebrae and one case had severe cervical kyphosis with compression of the spinal cord similar to that seen in the present case [Poznanski, 1994].

Therapeutic treatment with warfarin during pregnancy results in severe vitamin K deficiency in the embryo. This affects the normal formation of all vitamin K-dependent proteins. The effect on the blood clotting proteins of the embryo occurs in the second and third trimesters and can lead to pre- and post-natal bleeding. The effect on MGP and BGP can occur at any time after about 6 weeks of gestation but the consequences for the embryo are not proven. It is our current hypothesis that BGP, which is present in bone but not in cartilage, does not have an essential role in prenatal development. In contrast, MGP accumulates in the matrix of cartilage, bone and dentine and appears to be essential for normal development of cartilage. Its presence in the growth plates of bones suggests it has a role in the control of mineralization since over-mineralization of the growth plate is seen in warfarin-treated rats [Price et al., 1982; Howe and Webster, 1992]. Absence or reduction of functional MGP would make all cartilages susceptible to ectopic calcification. It is possible that ectopic calcification is the cause of reduced or abnormal growth of affected cartilages resulting in abnormal bone development in some cases. Exposure to warfarin in the first trimester has a particularly severe effect on the nasal septal cartilage, perhaps because of its rapid growth during this period. Any drug [Howe et al., 1992; Howe and Webster, 1994; Howe et al., 1995] or genetic disorder [Pauli et al., 1987] that causes vitamin K deficiency causes the same embryopathy as seen with warfarin.

Although in this report the patient had signs and symptoms of a spinal cord lesion dating from birth, it is possible that the excessive mobility of the spinal column contributed to further deterioration over the first few months of life. There is no certain evidence that such was the case but in view of the possibility future cases of the warfarin embryopathy should be assessed radiologically and neurologically early in the neonatal period and their neurological status should be monitored clinically. Where major cervical anomalies are detected, early magnetic resonance imaging of the spinal cord is appropriate.

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