Chondrodysplasia punctata after warfarin in early pregnancy

Case report and summary of the literature

M F WHITFIELD
Department of Paediatrics, University of Sheffield

SUMMARY A third case of chondrodysplasia punctata after exposure to warfarin alone in early pregnancy is described. The clinical course of the child during the first 18 months is outlined. The use of warfarin in early pregnancy must be avoided because of its established teratogenic effects in causing this syndrome, in addition to an overall increase in perinatal mortality.

Chondrodysplasia punctata is a disorder of growth, characterised by ectopic calcification of cartilage occurring either as a severe, lethal, rhizomelic form or as the milder Conradi-Hunerman type, for which no single aetiological factor has been found. 11 cases of the syndrome have been described associated with maternal warfarin ingestion in early pregnancy. This paper reports the third case of chondrodysplasia punctata in which warfarin was the only drug taken in early pregnancy and seems to support an aetiological relationship between the drug and the fetal abnormality.

Case report

The mother, a 21-year-old nulliparous white woman, was started on warfarin treatment, 10 mg daily, for deep venous thrombosis in the legs 10 weeks before conception. This dosage was continued until 20 weeks' gestation and then stopped. She remained well, free of infections, and was given no other drug during the pregnancy. At 33 weeks' gestation she developed hydramnios and premature labour, and a live female infant was delivered vaginally, weight 1·73 kg (10th centile), length 39 cm (<3rd centile), OFC 29·5 cm (10th centile). The trunk and limbs were short in relation to the head, there was brachydactyly, and the nose was small and squashed-looking owing to hypoplasia of the nasal bridge (Fig. 1). X-rays showed irregular stippled calcification of the bones of the feet, upper femora, and spine (Fig. 2), characteristic of chondrodysplasia punctata. Normal results were obtained for TSH, karyotype, IgM and serology for cytomegalovirus, toxoplasmosis, rubella, and syphilis.
Fig. 2 X-ray at one week showing stippled calcification in the bones of the feet, upper femora, and sacrum.

Table Clinical features of 11 cases of chondrodysplasia punctata associated with maternal warfarin

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Mother's age (years)</th>
<th>Birth weight (kg)</th>
<th>Length (cm)</th>
<th>Head circumference (cm)</th>
<th>Gestational age (weeks)</th>
<th>Nasal abnormality</th>
<th>Brachydactyly</th>
<th>Mental retardation</th>
<th>Sites of punctate calcification</th>
<th>Maternal drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerber et al.⁹</td>
<td>M</td>
<td>27</td>
<td>2.81</td>
<td>—</td>
<td>—</td>
<td>39</td>
<td>Yes</td>
<td>—</td>
<td>No</td>
<td>Information</td>
<td>Warfarin, digoxin, penicillin</td>
</tr>
<tr>
<td>Becker et al.¹⁰</td>
<td>F</td>
<td>22</td>
<td>2.275</td>
<td>47</td>
<td>33</td>
<td>39</td>
<td>Yes</td>
<td>Yes</td>
<td>Mild</td>
<td>Femoral, sacral, cervical vertebrae</td>
<td>Sulphasaxazole, warfarin, digoxin, erythromycin, frusemide, potassium supplements</td>
</tr>
<tr>
<td>Case 2</td>
<td>M</td>
<td>21</td>
<td>1.37</td>
<td>—</td>
<td>—</td>
<td>35</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>Calcaneus, phalanges, vertebral, sacral, digoxin</td>
<td>Warfarin, digoxin, diazepam, frusemide</td>
</tr>
<tr>
<td>Pettifor and Benson¹¹</td>
<td>M</td>
<td>36</td>
<td>2.5</td>
<td>—</td>
<td>—</td>
<td>38</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Warfarin, digoxin, frusemide, potassium supplements</td>
<td>Warfarin, digoxin, thiazide</td>
</tr>
<tr>
<td>Case 3</td>
<td>F</td>
<td>29</td>
<td>3.3</td>
<td>—</td>
<td>—</td>
<td>41</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Vertebral and sacral, femoral, ribs, nasal areas</td>
<td>Heparin, dipyridamole, digoxin, cephalaxin, doxycycline</td>
</tr>
<tr>
<td>Shaul et al.⁶</td>
<td>M</td>
<td>29</td>
<td>1.8</td>
<td>43</td>
<td>32.5</td>
<td>33</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Warfarin, calcanei only</td>
<td>Warfarin, tylanol</td>
</tr>
<tr>
<td>Pauli et al.¹²</td>
<td>F</td>
<td>33</td>
<td>1.6</td>
<td>—</td>
<td>—</td>
<td>32</td>
<td>Yes</td>
<td>—</td>
<td>No</td>
<td>Calcanei only</td>
<td>Warfarin, cephalexin, doxycycline</td>
</tr>
<tr>
<td>Richman and Lahman¹³</td>
<td></td>
<td>19</td>
<td>2.67</td>
<td>—</td>
<td>—</td>
<td>36</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Calcanei only</td>
<td>Warfarin, tylanol</td>
</tr>
<tr>
<td>†Abbott et al.²</td>
<td>M</td>
<td>29</td>
<td>1.2</td>
<td>35</td>
<td>27.5</td>
<td>31</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>All epiphyses, femoral, ribs, calcanei</td>
<td>Warfarin, Warfarin</td>
</tr>
<tr>
<td>Collins et al.³</td>
<td>F</td>
<td>33</td>
<td>1.59</td>
<td>—</td>
<td>—</td>
<td>32</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Femoral, rib, calcanei, vertebral</td>
<td>Warfarin, Warfarin</td>
</tr>
<tr>
<td>Present case</td>
<td>F</td>
<td>21</td>
<td>1.79</td>
<td>39</td>
<td>32.5</td>
<td>34</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Femoral, calcanei, vertebral</td>
<td>Warfarin, Warfarin</td>
</tr>
</tbody>
</table>

* Died at 3 min, † died at 21 days of life.
* Blind due to optic atrophy.
* Same case as that reported by DiSaia⁴.
From 4 days to 6 weeks of age she suffered from nasal obstruction, intermittently causing cyanosis and bradycardia. Some benefit was obtained from ephedrine nasal drops, repeated nasal suctioning, and placement of an oral airway. She was discharged home at 8 weeks weighing 3·12 kg, gaining weight and feeding reasonably well. During the next 6 months however, she was frequently readmitted to hospital because of feeding difficulties and respiratory distress produced by slight intercurrent respiratory infections. At a corrected age of 7 months her development was slow; she was not yet sitting and was reaching out for objects but not transferring from hand to hand. She developed meningocencephalitis after pertussis vaccination at 9 months.

When seen at a corrected age of 2 years she was alert and responsive, appeared intellectually normal on formal assessment, but had a slight right hemiparesis and atlanto-axial instability. She remains short with short limbs, but growth of the nasal passages has eliminated nasal symptoms and the external appearance of the nose is not obviously abnormal.

Discussion

This is the third case of chondrodysplasia punctata to be reported after ingestion of warfarin alone in early pregnancy,5–8 although 8 others have been reported in babies whose mothers had taken between 2 and 5 drugs during the first trimester (Table). All except one (Case 2; Becker et al.10) of these 11 cases were of the less severe Conradi-Hünerman type of chondrodysplasia punctata, 9 of the 11 surviving the neonatal period compared with a 50% mortality in the first year for cases not caused by warfarin.4 Hypoplasia of the nasal bridge is a common finding, producing significant nasal obstruction in 9 of the 11 cases. Nine of the 11 cases had stippled calcification of vertebrae, calcanei, and upper femora, and there was slight developmental delay in 2 out of 9.

Although a genetic aetiology has been suggested for chondrodysplasia punctata1 it has also been reported after a wide variety of potentially teratogenic factors.4 One series of 23 cases of the less severe form9 enumerated illness in the pregnancy, maternal anticonvulsant therapy in early pregnancy, and advanced paternal age as the most frequently identified potential causative factors. None of these mothers had had warfarin. Shaull et al.6 speculated that the teratogenic effects of warfarin may be related to bleeding into embryonic or fetal cartilage at a critical stage of development, with subsequent aberrant ectopic calcification and disordered cartilage growth. Optic atrophy, microcephaly, and cerebral agenesis have also been described.8 The fetuses of mothers requiring anticoagulation during pregnancy are exposed not only to the risk of anticoagulation but also to adverse perinatal factors related to the maternal indication for anticoagulation. The perinatal mortality rate of one in 38 among a heparin-treated group of pregnancies8 compares favourably with the rate of one in 5 in two studies of warfarin-treated patients,7–8 suggesting that warfarin per se is an additional hazard.

There appears now to be convincing evidence that warfarin in early pregnancy is a cause, albeit rare, of chondrodysplasia punctata, that it tends to produce the less severe form of the disorder with better perinatal survival and long-term prognosis, that it produces an overall increase in perinatal mortality rate, and that it must be avoided in early pregnancy and in the potentially pregnant.

I thank Professor R D G Milner, Dr L S Taitz, and Dr J A Black for permission to report a case under their care.

References

Referees 1979

We continue to depend heavily on the help we get from our referees who assess and, in many cases, suggest significant improvements to the papers. This is the only opportunity we have to acknowledge publicly the work done by them during the past year.

P Ackett
Barbara M Ansell
G C Arneil
A Aynsley-Green
Gillian Baird
N D Barnes
J D Baum
J F R Bentley
H Bickel
B D Bower
R D H Boyd
P T Bray
C G D Brook
J K Brown
J M H Buckler
D Burman
N R Butler
C Chantler
Judith M Chessells
C Clarke
Barbara Clayton
F Cockburn
K W Cross
D P Davies
Pamela A Davies
J A Davis
J A Dodge
M A P S Downham
V Dubowitz
J A Dudgeon
P M Dunn
E J Ebrahim
H Eckstein
Dorothy F Egan
J L Emery
P Evans
J W Farquhar
J A Fixsen
C D R Flower
J O Forfar
Gillian Gandy
J F T Glasgow

Correspondence to Dr M F Whitfield, Department of Paediatrics, Children's Hospital, Western Bank, Sheffield S10 2TH.

Received 27 February 1979