Chondrodysplasia punctata and maternal systemic lupus erythematosus

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In this issue, Elcioglu and Hall1 and Austin-Ward et al2 have both described infants with chondrodysplasia punctata (CP) and maternal systemic lupus erythematosus (SLE). Elcioglu and Hall1 further point out that Costa et al3 and Mansour et al4 had also described infants with CP and maternal SLE, so the occurrence of these two conditions becomes highly unlikely to be coincidental, but rather causal in some fashion, with maternal SLE somehow involved in the occurrence of CP in the exposed infant.

It must first be reiterated that CP is a finding, not a diagnosis, and as such can have numerous causes, which are well reviewed by Wulfsberg et al5 and Poznanski.6 Vitamin K involvement is the common thread in the pathogenesis of several conditions with CP, with these conditions including warfarin embryopathy, vitamin K epoxide reductase deficiency, and maternal malabsorption leading to vitamin K deficiency; however, it is almost certainly not the only mechanism whereby CP can develop. Although Howe et al6 had postulated a role for abnormal vitamin K metabolism in phenytoin teratogenesis (in which CP can also occur), more recently Danielsson et al7 have suggested embryonic hypoxia/ischaemia secondary to embryonic bradycardia induced by phenytoin as the pathway which causes phenytoin teratogenesis. Franco et al8 described mutations in arylsulfatase E in patients with X linked recessive CP, and in the same issue of Nature Genetics, Purdue et al9 assert that deficiency of the human homologue of the yeast PEX7 gene causes rhizomelic CP, whereas Chang et al10 describe human homologue of PEX12 mutations in peroxisome biogenesis disorders, which include several entities with CP (see also editorial by Subramani11). The mechanism whereby these abnormal gene products produce CP, as well as the other phenotypic manifestations of the condition, is not yet well understood. Another condition associated with CP is Conradi-Hunermann syndrome, which is thought to be caused by a lipid metabolic defect12; this is intriguing in light of the finding of CP in some children with Smith-Lemli-Opitz syndrome, which is caused by a defect in 7-dehydrocholesterol metabolism. In yet other conditions in which CP can occur (for example, trisomies 18 and 21, fetal alcohol or rubella syndrome), no pathogenetic pathway has been found. It is therefore an understatement that there are numerous ways in which CP can be induced to occur in the fetus, and thus it should not be surprising that maternal SLE is yet another cause of CP in the exposed infant.

But how does SLE cause, or contribute to, the occurrence of CP? It is known that patients with SLE are prone to develop hypoprothrombinaemia secondary to lupus anticoagulant and acquired factor II deficiency13; this is intriguing in that at one time haemorrhage was thought to be the mechanism which caused CP. Other antibodies, such as IgG anticardiolipin and anti-B2-glycoprotein I, have been implicated in the development of thrombosis in SLE patients.14 Furthermore, there is an association of platelet autoantibodies with major histocompatibility complex class II alleles,15 suggesting genetic differences for the likelihood of developing thrombosis or thrombocytopenia as a complication of SLE. This is pertinent in that there are almost certainly genetic factors which must be present in order for the CP to occur; this is shown by both the apparent rarity of the occurrence of CP in children born to women with SLE, and yet the occurrence in sibs as described by Elcioglu and Hall.1 However, before we can fully understand the pathogenesis involved, it is important to determine the frequency of CP in children whose mothers have SLE during pregnancy, whether there are any common denominators (such as certain antibody profiles) in women whose children are affected, and how these factors could affect bone and cartilage development. In turn, this research could lead to a better understanding of how CP is caused by other prenatal exposures or genetic syndromes, thus giving us insights into the various pathogenetic mechanisms.

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