Cardiac defects in the children of mothers with high concentrations of plasma phenylalanine

Postnatal brain damage in a homozygous affected child with phenylketonuria is well recognised. Less well known, despite its recognition over thirty years ago, is the damage that even a heterozygous fetus can incur in a homozygous mother with high blood concentrations of phenylalanine. Low birth weight, microcephaly, mental retardation, and congenital heart disease are most often seen but other defects of structure have been reported. Lenke and Levy in their retrospective survey found congenital heart disease in 12–15% of the offspring of untreated mothers with classic phenylketonuria. Typically these women had phenylalanine concentrations in excess of 1200 μmol/l, more than 15 times the normal value. Because the placenta transports amino acids actively, fetal blood concentrations are higher than those in the mother—with the ratio of fetus to mother for phenylalanine being around 1.6. There is evidence too that high maternal phenylalanine values may decrease the transfer of some other amino acids across the placenta so that the fetus may have immensely high concentrations of phenylalanine but be relatively deficient in some other amino acids. Similarly, in animals there is evidence that high fetal blood concentrations of phenylalanine may interfere with the transport of other amino acids through the blood brain barrier into the central nervous system. Poor fetal growth, low birth weight, microcephaly, and mental retardation may all be ascribed to the resulting amino acid imbalances quite apart from other possible toxic effects of phenylalanine or its metabolites.

The sensitivity of the postnatal brain to high concentrations of phenylalanine has been known for decades. Congenital heart disease, however, is different. The congenital cardiac abnormalities are classic defects of organogenesis that can be traced back to the fifth to eighth weeks of fetal life during which the heart develops from a simple tube into a four chambered structure with separate atrioventricular canals and separate outflow tracts developing from the common truncus arteriosus. The congenital defects in maternal phenylketonuria have included coarctation of the aorta, hypoplastic left ventricle, mitral valve atresia, ventricular septal defects, Fallot’s tetralogy, and now, as reported on page 180 of this issue, an anomalous coronary artery. There are some major unanswered questions. For example, is any particular pattern of congenital cardiac defects commoner in maternal phenylketonuria? Why should the heart apparently be the next most vulnerable organ in the fetus after the central nervous system? The incidence of mental retardation in untreated maternal phenylketonuria when the mother’s phenylalanine exceeds 1200 μmol/l is around 90%, and the incidence of microcephaly only slightly less. These incidences are much higher than that of congenital heart disease but the question of unexpected cardiac susceptibility remains.

One theory relates to a link between the developing central nervous system and the embryonic heart. Kirby and Miyagawa have drawn attention to the evidence that neural crest cells are important for normal cardiac development.7 The neural crest cells migrate away from the neural plate as it closes to form the neural tube. Incidentally, a higher incidence of neural tube abnormalities has not yet been reported in the offspring of mothers with phenylketonuria. Cranial neural crest cells move during normal embryonic development into the pharyngeal arches and pharyngeal region. Some of these, the cardiac neural crest cells, have been identified in association with the aortic arch arteries and the developing outflow tract. Studies of neural crest ablation in developing chick embryos produced various cardiac anomalies and it seems that migrating neural crest cells are critical in the control of cardiac development. Could congenital cardiac damage in maternal phenylketonuria ultimately be the result of another adverse effect on cells of neural plate origin—in addition to the adverse effects on the same tissue that lead to microcephaly and mental retardation? Unifying hypotheses are always attractive. Proof is more difficult. Other defects of organogenesis—such as oesophageal atresia—have been described in the offspring of mothers with phenylketonuria8 but whether these can be linked to an adverse effect on neural crest cells has not been suggested and indeed it is not clear whether these defects are truly more common than in the normal population. Proof that maternal phenylalanine in some way adversely affects the fetal heart through an effect on neural crest cells will need experimental work in animals that closely models the human biochemical defect. Work on that has started.
Whatever the theoretical aspects of the problem some practical issues are already clear. Naughten and Saul reported three deaths in infancy in their series of 50 offspring born to mothers with phenylketonuria, two of which were caused by congenital heart disease. I know of two deaths from congenital heart disease in a series of only 12 offspring. It is a serious problem which cannot be prevented unless the mother's blood concentration of phenylalanine is lowered before the start of cardiac development. It is too late to start dietary measures when a woman is 7 weeks pregnant. In practice this means a pre-conception diet and a planned pregnancy when the mother's phenylalanine is low. The deaths referred to above all occurred when a strict diet was started after conception. There is already evidence that a pre-conception diet lowers the incidence of congenital heart disease. Lenke and Levy found no cases of congenital heart disease in 44 offspring of mothers with phenylalanine values below 600 μmol/l and Drogari et al found no examples of congenital heart disease in 17 offspring after a strict diet had been started before conception.

For the cardiologist there is great theoretical interest in the mechanisms of congenital heart disease, and maternal phenylketonuria may offer unique insights into such problems. From a practical point of view it is worth screening all mothers of children with congenital heart disease for maternal phenylketonuria? This depends on whether undiagnosed maternal phenylketonuria exists in the population. Before the advent of widespread neonatal screening around 1970–1972 cases of phenylketonuria were definitely missed. Most of these individuals became intellectually impaired as a result; so mothers of low IQ who have a child with congenital heart disease should be tested for phenylketonuria. A small number of women in whom phenylketonuria was not diagnosed in early life did achieve IQ values in the normal range. For this reason if a child has both congenital heart disease and other suggestive clinical features such as microcephaly or low IQ it is worth testing the mother for phenylketonuria regardless of her IQ. Finally, because it is clear that the risk of damage extends to all offspring of a mother with phenylketonuria if it is untreated by diet any mother with more than one child with congenital heart disease must be tested for raised plasma phenylalanine.

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1 Dent CE. Relation of biochemical abnormality to development of mental defect in phenylketonuria. Etiological factors in mental retardation. 23rd Ross Pediatric Research Conference, November 1956, Columbus, Ohio, p.32, 1957.