

Teratogenic inborn errors of metabolism

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Summary: Most children with inborn errors of metabolism are born healthy without malformations as the fetus is protected by the metabolic activity of the placenta. However, certain inborn errors of the fetus have teratogenic effects although the mechanisms responsible for the malformations are not generally understood. Inborn errors in the mother may also be teratogenic. The adverse effects of these may be reduced by improved metabolic control of the biochemical disorder.

Chromosomal disorders are responsible for many dysmorphic syndromes (De Grouchy & Turleau, 1984) and, since the teratogenicity of thalidomide was recognized, the potential toxicity to the fetus of drugs given to the mother has also received much attention. Dysmorphic syndromes are now well described in children whose mothers have taken hydantoins, methotrexate, alcohol, and warfarin (Shepard, 1983). Many other drugs are under suspicion.

By contrast, it has been standard teaching that babies with inborn errors of metabolism are normally formed and healthy at birth because the fetus is protected by the exchange of nutrients and metabolites across the placenta. Only after birth does the disorder become evident. However, this is not correct as inborn errors in the fetus and in the mother may be teratogenic.

Inborn errors of the fetus

The fetus is only partially protected from the injurious effects of many inborn errors by the placenta. *In utero* catabolic pathways are relatively inactive so that metabolites are likely to be formed only slowly, if at all. However, if they are formed, removal may be even slower so that toxic metabolites accumulate. The rapidly growing tissues of the fetus are likely to be particularly vulnerable to any adverse effect of such compounds.

3-Hydroxyisobutyryl CoA deacylase deficiency

In 1982 Brown *et al.* reported a child who had died of multiple congenital abnormalities with abnormal facial features, tetralogy of Fallot, multiple vertebral abnormalities and agenesis of the corpus collosum. A

chromosomal disorder was suspected but the karyotype was normal. Fortunately urine was examined for metabolic abnormalities and two unusual compounds were detected, 2-carboxypropyl conjugates of cysteine and cysteamine. These were shown to be derived from ethylacrylyl CoA that accumulated because of an inborn error of the catabolism of valine. Methylacrylyl CoA is a highly reactive compound forming conjugates spontaneously with compounds containing free sulphydryl groups, and methylacrylate esters have been shown to be potent teratogens in rats (Singh *et al.*, 1972) causing skeletal abnormalities similar to those noted in the patient. Although free methylacrylyl CoA could not be detected and the concentration of the conjugates was low, the quantities present in the tissues of the fetus were thought to have caused the malformations.

Multiple acyl CoA dehydrogenase deficiency

In one of the early descriptions of multiple acyl CoA dehydrogenase deficiency (also known as glutaric aciduria type II) the baby was noted to have dysmorphic features including large head with bulging fontanelle, low set ears, small palpebral fissures, short nose with long philtrum, bilateral simian creases, dysplastic nails and polycystic kidneys (Sweetman *et al.*, 1980). The patient developed a metabolic acidosis and hypoglycaemia, dying at the age of 24 hours. Numerous abnormal metabolites including glutaric, ethylmalonic, isovaleric, isobutyric and several other dicarboxylic acids were detected in the urine. Other patients with the same biochemical disorder have now been described (Goodman & Frerman, 1984), some of whom have similar dysmorphic features (Goodman *et al.*, 1983; Bohm *et al.*, 1982). The disorder is caused by deficiency of several acyl CoA dehydrogenases (Lehnert *et al.*, 1982). The only biochemical difference between the dysmorphic and the non-dysmorphic

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patients is that sarcosine is present in the non-dysmorphic patients but has not been found in the dysmorphic ones. However this is unlikely to be important (Goodman & Frerman, 1984). The organic acids appear to be similar and no teratogenic compounds have been identified.

Zellweger's syndrome

In 1964 Zellweger and his colleagues (Bowen *et al.*, 1964) described the syndrome characterized by a typical facial appearance with a tall forehead, slanting eyes, epicanthic folds and a large fontanelle in association with marked hypotonia, severe mental retardation, disturbed liver function and eye abnormalities. Goldfischer *et al.* (1973) showed that peroxisomes were not present in the liver of these patients and it has now been shown that the membrane-bound enzymes normally present in the organelles are deficient (Wanders *et al.*, 1984). The typical biochemical consequences are a severe deficiency of plasmalogens (Heymans *et al.*, 1983), and accumulation of very long chain fatty acids (Brown *et al.*, 1982), phytanic acid (Poulos *et al.*, 1984), pipecolic acid (Govaerts *et al.*, 1982), and abnormal C-27 bile acids (Mathis *et al.*, 1980). Now that the biochemical basis of the disorder is clearer it has become apparent that there is wide phenotypic variation. Patients are probably always retarded and hypotonic but the dysmorphic features and the eye manifestations are varied (Govaerts *et al.*, 1982). This has led to the recognition that several other syndromes including infantile Refsum's disease (Poulos *et al.*, 1984), neonatal adrenoleukodystrophy (Brown *et al.*, 1982), trihydrocoprostanic acidemia (Parmentier *et al.*, 1979) are probably all variants of the Zellweger's syndrome. So far the biochemical abnormalities in these disorders appear to be similar to those in classical Zellweger's syndrome and at present there is no explanation for the wide variation in expression.

The spectrum of peroxisomal disorders has been extended still further as Heymans and his colleagues (1985) have shown that in rhizomelic chondrodysplasia punctata peroxisomes are absent or abnormal morphologically with defective activity of certain peroxisomal enzymes.

DOOR syndrome

DOOR syndrome is an autosomal recessive disorder that is characterized by deafness, nail dystrophy, abnormal facies and mental retardation (Cantwell, 1975). The patients often have a severe seizure disorder. Patton and his colleagues (1984) have recently described three patients with this disorder who excreted a marked excess of 2-oxoglutarate in the urine. No other biochemical abnormalities have been found and it is not yet known whether this is a primary or

secondary finding. Enzyme studies have been normal.

The number of inborn errors that cause dysmorphic syndromes is still very small and in only one inborn error has a compound been identified which could be responsible for the malformation. However the principle is established that inborn errors of the fetus can be responsible for dysmorphic changes and biochemical abnormalities should continue to be sought in dysmorphic patients with autosomal recessive disorders. However, the compounds responsible for the teratogenic effects may only be present at low concentration and easily overlooked with the screening methods in current use, in contrast to many inborn errors in which there is gross accumulation of metabolites. In Zellweger's syndrome there is failure of synthesis of plasmalogens, a major phospholipid component of cellular membranes as well as the accumulation of other compounds. Thus in some disorders failure of synthesis could be responsible for malformations.

Inborn errors of the mother

An inborn error that causes only minor problems in the adult may cause serious abnormalities in the developing fetus.

Phenylketonuria

Patients with phenylketonuria (PKU) have a deficiency of phenylalanine hydroxylase so that they are unable to convert phenylalanine to tyrosine. Consequently phenylalanine accumulates and tyrosine concentrations are reduced; indeed tyrosine becomes an essential amino acid. At birth, babies with PKU are normal. Without treatment the majority will become severely mentally retarded (Koch *et al.*, 1974) but with early diagnosis through neonatal screening and treatment with a strict low phenylalanine diet, progress during childhood is good with the mean IQ close to the population mean (MRC/DHSS Phenylketonuria Newsletter, 1980). The aim is to maintain the plasma phenylalanine concentration between 100–500 $\mu\text{mol/l}$ but strict control is difficult to maintain and the diet is now usually relaxed during late childhood and adolescence. The plasma phenylalanine concentration is allowed to rise up to 1200 $\mu\text{mol/l}$. Further relaxation of the diet is common so that by adult life patients are often on a more or less normal diet with plasma phenylalanine concentrations in excess of 1500 $\mu\text{mol/l}$.

The offspring of females whose phenylalanine concentrations are above 1200 $\mu\text{mol/l}$ during the pregnancy have a high incidence of microcephaly and mental retardation (Lenke & Levy, 1980). Other abnormalities include cardiac defects such as tetralogy

of Fallot and ventricular septal defect, hypotonia and a dysmorphic appearance similar to that of the fetal alcohol syndrome (Lipson *et al.*, 1981). The risk of microcephaly and mental retardation at lower phenylalanine concentrations is less but in one study, even for those mothers whose highest recorded plasma phenylalanine concentration was between 180–600 $\mu\text{mol/l}$, between 20–25% of the offspring had mental retardation and microcephaly, a fourfold increase above that expected (Lenke & Levy, 1980). This estimate is probably too high because of the method of ascertainment and in another study the risk of mental retardation and microcephaly when cord blood phenylalanine was less than 1100 $\mu\text{mol/l}$ was low (Levy & Waisbren, 1983). The conclusion from these apparently contradictory observations is most probably that the risk to the fetus is directly related to the maternal phenylalanine concentrations, being very high above 1200 $\mu\text{mol/l}$ and decreasing, but not negligible, at lower phenylalanine levels.

Reintroducing the strict diet once pregnancy has been confirmed does not prevent the abnormalities (Lenke & Levy, 1980). In a number of pregnancies diet has been started before conception and in almost all cases the outcome has been normal although not invariably so (R. Koch, personal communication). The current practice is that if a mother is intending to have a child, she should go back on the diet before conception aiming to keep plasma phenylalanine concentrations below 500 $\mu\text{mol/l}$.

Ornithine carbamoyl transferase deficiency

Ornithine carbamoyl transferase deficiency (OCTD) is the most common of the inborn errors of the urea cycle and is an X-linked disorder (Walser, 1983). Affected boys usually, but not invariably, have very low enzyme activity and present in the neonatal period with severe hyperammonaemia. By contrast the clinical expression in females, even within one kindred, is very varied; some develop hyperammonaemia in childhood and others have no symptoms at all. This marked variation is a consequence of Lyonization, the process of inactivation of one X chromosome in a cell at an early stage in fetal development. The tissues, therefore, contain two populations of cells, each with one X chromosome active. Since the process is random, the composition of tissues will vary between individuals. In OCTD the patients' symptoms will depend on the relative proportion of the two populations of liver cells. Many females will have no symptoms but nevertheless will be carriers and at risk of having boys with severe disease. Although the carriers may have few clinical symptoms, their IQ may be lower than expected (Batshaw *et al.*, 1980) and the disorder may be responsible for abnormalities in the developing fetal brain.

Harding *et al.* (1984) studied the brains of children with OCTD and found evidence of abnormalities in the brain that were of prenatal origin. One boy who died in the neonatal period and whose mother was an asymptomatic carrier had widespread histological changes with poor myelination and marked spongy change in the deep white matter of the cerebral hemispheres. Cerebellar heterotopias were also present. In a girl who died at the age of 13 months there was extensive brain destruction with good evidence that it had begun *in utero*. The mother had had severe hyperemesis throughout her pregnancy and during a protein load she vomited. Despite this her plasma ammonia rose to 102 $\mu\text{mol/l}$. It was suggested that this carrier mother had had marked biochemical abnormalities during her pregnancy that had initiated the brain damage in the fetus.

Ammonia is highly toxic to the brain and hyperammonaemia after birth often causes severe cerebral damage and death (Msall *et al.*, 1984). However, ammonia is not the only potentially teratogenic factor. Arginine is not an essential aminoacid in normal individuals because it can be synthesized in the urea cycle. In patients with inborn errors of this pathway, synthesis of arginine is reduced so it becomes an essential aminoacid (Brusilow, 1984). Deficiency may develop during pregnancy with increased demands and may be a factor in prenatal damage. For these reasons it has been recommended that the dietary intake of protein, plasma ammonia and aminoacids should be monitored during pregnancy of carrier females and, if any abnormality is detected, it should be corrected (Pembrey *et al.*, 1985).

Diabetes mellitus

Although diabetes mellitus is not usually inherited in a simple Mendelian fashion it is nevertheless a metabolic disorder with a genetic component. Infants of mothers with diabetes have an increased incidence of many congenital anomalies involving the cardiovascular and skeletal system most commonly but also the genito-urinary, gastro-intestinal and central nervous systems (Pedersen *et al.*, 1964; Soler *et al.*, 1976). The caudal regression syndrome (Passarge & Lenz, 1966) and related disorders such as femoral hypoplasia-unusual facies syndrome (Burn *et al.*, 1984) may be the most specific although only a proportion of patients with these disorders are born to mothers with diabetes.

The risk of malformations is higher in those diabetics who have had the illness for longer and in those with established vascular disease (Pedersen *et al.*, 1964). Prediabetic women do not have any increase in risk so it is probable that it is the diabetes and not other genetic factors that is responsible for the teratogenic effect (Bennett *et al.*, 1979). Good control of the diabetes is thought to reduce the incidence of

congenital anomalies in both man and experimental models (Baker *et al.*, 1981; Miller *et al.*, 1981).

Although the precise mechanisms of the damage have not been elucidated in any of the maternal disorders, good metabolic control from conception throughout the pregnancy will reduce significantly the risk to the fetus.

Interaction of drugs and enzyme variations

Both the therapeutic and toxic effects of drugs may be influenced by genetically determined variations in the activity of enzymes responsible for drug metabolism. The differences may also be one factor contributing to the teratogenicity of some drugs as a reduction in the rate of some reactions could lead to the accumulation of toxic metabolites *in utero*.

The risk of malformation in patients taking phenytoin and other hydantoins is between 7–15% (Hanson *et al.*, 1976; Shepard, 1983). These drugs are normally metabolized by the P450 system to form an arene oxide which is then hydroxylated by epoxide hydrolase. If the activity of this enzyme is reduced the epoxide would be liable to accumulate in tissues. The intermediate oxide is a highly reactive compound that will bind to cellular proteins and DNA thereby becoming a potential teratogen.

In a recent remarkable case dizygotic twins were

exposed to phenytoin but only one developed hydantoin syndrome (Buehler, 1985). Enzyme studies showed that the activity of the epoxide hydrolase was greatly reduced in the affected twin. Both twins were exposed to the same concentration of phenytoin but because of the lower activity of the epoxide hydrolase in the affected fetus it was postulated that there was a greater accumulation of the oxide which was responsible for the 'syndrome'.

Conclusions

Until recently inborn errors appeared to have little relevance to teratology but the disorders described have altered this view. Compounds may be formed *in utero* that are teratogenic and are not necessarily readily detectable with current screening methods. This may be extended since metabolites may be formed (or not synthesized) at critical periods of development but the biochemical abnormality may be difficult to identify post-natally because of differences in metabolic pathways. Thus many more recessive dysmorphic syndromes may have a biochemical basis which has not yet been discovered because no simple metabolic defect can be detected.

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