Drug induced VATER association: is dibenzepin a possible cause?

The VATER complex is a non-random combination of three or more vertebral, anorectal, tracheo-oesophageal, radial, and renal anomalies of a co-terminally normal child. Cardiac abnormalities are sometimes also involved (VACTERL). It has not been recognised as a specific syndrome and its components are varied and aetiological factors remain unclear. Some studies in their population based study, emphasised the aetiological heterogeneity of the entity. Exposure to proges- togen or oestrogen or both in the first trimester of pregnancy has been suggested as a possible cause and, recently, lead intoxication and lovastatin administration have also been implicated. We describe the first case of VACTERL association in a neonate whose mother had been treated with dibenzepin.

The proband is the second child of a 25 year old woman who suffered from depression and had been treated with dibenzepin (Victoril) (80 mg x 3/day) throughout her pregnancy. The mother did not smoke or drink alcohol or coffee, and had not suffered from any infection during pregnancy. The parents are not related, and the father is healthy. The family history was unremark- able. The mother had not taken any medica- tion during her first pregnancy and gave birth to a normal baby. After delivery, she was treated with a second antidepressant, and, recently, with lovastatin. During the second pregnancy (1992), ultrasound and x-ray measurements were not performed. The fetal heart rate near term showed normal findings.

The 40 week term infant, born in February 1993, with a weight appropriate for gesta- tional age (3260 g), presented with oesopha- geal and tracheal atresia, lumbosacral hemivertebrae, dextroposition of the heart, and right cryptorchidism. Brain and kidney ultrasound were normal. Karyo- type analysis and chromosome studies were normal. The oesophageal malformations were surgically corrected by end to end anastomosis and fistulotomy. At the age of 3 months, physical and neurological development was normal.

Dibenzepin is a tricyclic antidepressant, rarely used during the first trimester. Because of the very limited data on dibenzepin usage in pregnancy, a precise risk estimation cannot be performed.

It is noteworthy that neither extensive epidemiological studies in humans nor experimental data have shown clear evidence of an association between the use of tricyclic antidepressants in pregnancy and birth de- fects, and the teratogenic effect of these drugs remains uncertain and contradictory. The VATER complex is one of the more common patterns of multiple malformations in newborns. Prenatal exposure to exogenous sex hormones, lead, and, recently, lovastatin might have a teratogenic effect. Although it is impossible to establish a causal relationship between prenatal dibenzepin ex- posure and VATER on the basis of a single case report, the present report adds another possible teratogenic agent and raises the pos- sibility of a drug induced type of VATER complex. A large prospective multicentre collaborative study is needed to clarify this issue further.

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Kyphomelic dysplasia

A six year follow up of a child with kypho- melic dysplasia has shown some interesting and previously undescribed features. This case was originally described by Temple et al.

Kyphomelic dysplasia is a rare condition with a generalised abnormality of skeletal growth. It is characterised by rachitomelic and mesomelic limb shortening with short, broad, and bowed long bones, the femora being most severely affected. There is meta- physeal flaring and irregularity in infancy, causing prominent joints with restricted mobility. The ribs are short and flared. Variable features include micrognathia, midface hypoplasia, long philtrum, facial haemangioma, abnormal rib number, mild platyspondyly, increased acetabular angles, and skin dimples over bony prominences.

To date 11 cases of kyphomelic dysplasia have been reported.

The subject, a male child, remained mildly dysmorphic at the age of 3 years 3 months. Rachitomelic shortening of the limbs with anterior bowing of the thighs was still evident, but had improved since infancy. His gait was normal with a tendency to toe walk on the left and he began to complain of intermitt- ent left back pain. A radiograph showed flattening and fragmentation of the right capital femoral epiphysis (figure) consistent with Perthes disease.

When he was 6 years old he complained of left hip pain and radiographs showed bi- lateral changes of avascular necrosis of the capital femoral epiphysis. A bone scan per- formed as one of the investigations for Perthes disease showed a hydropnephrotic right kidney. Further investigations showed the cause to be obstruction at the level of the vesicoureteric junction.

Changes in the hip which are similar to those in Perthes disease but always symmet- rical are found in certain skeletal dys- plasias and malformation syndromes, such as multiple epiphyseal dysplasia, mucopolysaccharidosis type IV, and trichorhinobopal- geal syndrome.

The aetiology of Perthes disease is thought to be multifactorial. The bony changes are those of avascular necrosis owing to inter- ruption of the blood supply to the capital femoral epiphysis. An increased incidence in congenital dislocation of the hip supports a traumatic aetiology.

We believe that abnormal gait, as in this child, is likely to result in stress injury resulting in avascular necrosis of the developing femoral head. It is likely that other syn- dromes with severe bowing of the femora may be associated with Perthes disease.

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Velocardiofacial syndrome and DiGeorge sequence

I was interested to read the series of articles published in the Journal of Medical Genetics regarding phenotypic overlap of the velocardo- diofacial syndrome and DiGeorge sequence, preceded by Judith Hall’s Editorial advocating the use of the acronym CATCH 22, as suggested by Wilson et al. The attention to velocardiofacial syndrome and 22q11 is very exciting and the authors are to be congratu- lated on this collective body of material.

I would like to respond to a number of points which, in my opinion, point out the important role of clinical diagnosis, even in conditions where molecular analysis has yielded positive results. The article of Greenberg, Goldmuntz et al, Driscoll et al.
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