LETTERS TO THE EDITOR

Drug induced VATER association: is dibenzipin a possible cause?

The VATER complex is a non-random combination of three or more vertebral, anorectal, tracheo-oesophageal, radial, and renal anomalies of unknown aetiology. Cardiovascular abnormalities are sometimes also involved (VACTERL). It has not been recognised as a specific syndrome and its components are viewed as a random occurrence. The VATER complex is a population based study, emphasised the aetiological heterogeneity of the entity. Exposure to progesterone 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 dibenzipin.

The proband is the second child of a 25 year old woman who suffered from depression and had been treated with dibenzipin (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 unremarkable. The mother had not taken any medication during her first pregnancy and gave birth to a normal girl in 1988. During the second pregnancy (1992), ultrasound and fetal heart rate measurements were not performed. The fetal heart rate near term showed normal sinus rhythm.

The 40 week term infant, born in February 1993, with a weight appropriate for gestational age (3260 g), presented with oesophageal atresia, tracheo-oesophageal fistula, lumbarosacral hemivertebrae, dextroposition of the heart, and right cryptorchidism. Brain and kidney ultrasound were normal. Karyotype and chromosomal studies were normal. The oesophageal malformations were surgically corrected by end to end anastomosis and fistulectomy. At the age of 3 months, physical and neurological development was normal.

Dibenzipin is a tricyclic antidepressant, rarely used during the first trimester. Because of the very limited data on dibenzipin use 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 defects, 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 dibenzipin exposure and VATER on the basis of a single case report, the present report adds another possible teratogenic agent and raises the possibility 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 kyphomelic 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 rhizomelic and mesomelic limb shortening with short, broad, and bowed long bones, the femora being most severely affected. There is metaphyseal 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 asplenia, 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. Rhizomelic shortening of the limbs with anterior bowing of the thighs was still evident, but had improved since infancy. His gait was abnormal with a tendency to toe walk on the left and he began to complain of intermittent low 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 bilateral changes of avascular necrosis of the capital femoral epiphysis. A bone scan performed as one of the investigations for Perthes disease showed a hydronephrotic 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 symmetric are found in certain skeletal dysplasias and malformation syndromes, such as multiple epiphyseal dysplasia, mucopolysaccharidosis type IV, and trichorhinophalangeal syndrome.

The aetiology of Perthes disease is thought to be multifactorial. The bony changes are those of avascular necrosis owing to interruption 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 syndromes 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 velocardiofacial syndrome and DiGeorge sequence, preceded by Judith Hall's Editorial advocating the use of the acronym CATCH22, as suggested by Wilson et al. The attention to velocardiofacial syndrome and 22q11 is very exciting and the authors are to be congratulated 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 articles of Greenberg, Goldmuntz et al., Driscoll et al.,

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Wadey et al., Burn et al., Holder et al., and Wilson et al. devote considerable attention to the overlap of a number of conditions, including velocardiofacial syndrome, DiGeorge sequence, and conotruncal anomaly face syndrome. These authors do not mention other conditions, such as velocardiofacial syndrome in patients with overlapping phenotypes, including those by Strong and Siedlakova. As we pointed out in our earlier article (Lett Med Genet 1993;30:822-6) the autosomal dominant inheritance of heart anomalies clearly had velocardiofacial syndrome. In Siedlakova's series of cases, many, but not all, of the cases shown had phenotypic features consistent with velocardiofacial syndrome. Reviews of photographs shown in other articles also show the classic phenotype of velocardiofacial syndrome, such as cases shown in Kaplan's description of occult submucous cleft palate. What all of these cases help to illustrate is the familiar parable of the five blind men and the elephant. Many clinicians who most frequently encounter DiGeorge have described from a variety of perspectives what may be a single class of patients. If one believes that heart anomalies are the primary defect, DiGeorge syndrome may be considered a nosological necessity of primary significance, whereas if one studies children with craniofacial anomalies, velocardiofacial syndrome may be of prominence. The problem relative to nosology is the absence of rigorous standards for clinical description and diagnosis. Often, those who focus attention on cardiac or immunological disorders might do so at the expense of other anomalies, such as speech disorders, minor limb anomalies, or eye findings. In our series of patients with velocardiofacial syndrome, we have attempted to be as rigorous as possible in describing all of the clinical manifestations in our patients. This is, in part, an outgrowth of the interdisciplinary nature of this Center (and others like it) which calls on 26 disciplines in the evaluation process. It was obvious to us long ago that a number of genetically non-specific disorders such as Robin, DiGeorge, and CHARGE occurred as secondary sequences to velocardiofacial syndrome. Included in the over 40 clinical features that may be associated with velocardiofacial syndrome are findings consistent with Robin, DiGeorge, and CHARGE, as well as other more obscure disorders, such as the so-called Siedlakova syndrome. As pointed out by Stevens et al., there is little doubt that the familial cases of DiGeorge which have been reported actually represent velocardiofacial syndrome.

The importance of accurate clinical description and diagnostic identification of velocardiofacial syndrome (or any other disorder, for that matter) is clearly illustrated by the articles of DiGeorge et al. They report a prevalence of 76% 22q11 deletions in patients referred to them as velocardiofacial syndrome. In other words, the diagnosis was applied by several different clinicians without an outing the validity or reliability of the clinical diagnostic technique used to reach that conclusion. Therefore, this prevalence statistic is essentially meaningless. Rigorous statistics demands the accuracy of scientific observations, and without proper assessments of that accuracy the observations can not be accepted as true. It should be mentioned that we have our own series of cases for molecular analysis to Dr Scambler's laboratory, there was a 100% prevalence of 22q11 deletion. It should also be mentioned that not all of those cases had heart anomalies, and few meet all the criteria of DiGeorge. In another series analysed by Dr Driscoll's laboratory, all of the cases successfully analysed were deleted except for one who had not been formally reviewed as previously noted in 1987. On subsequent clinical examination at the age of 6 years in 1993, it became obvious that this patient did not have velocardiofacial syndrome. In fact, it was the coincidence of Robin sequence and a 22q11 microdeletion that led to the diagnosis in the neonatal period. With growth and time, it became obvious that we were incorrect in our earlier diagnosis. Additional cardiac evaluation after the diagnosis showed anomalies not consistent with velocardiofacial syndrome. Therefore, in our experience, clinical application of the diagnosis of velocardiofacial syndrome by careful analysis (preferably longitudinal) of clinical phenotype has led to a 100% accurate detection of a 22q11 microdeletion in all cases.

The 83% prevalence of DiGeorge cases deleted at 22q11 as reported by Driscoll et al. may reflect the aetiological heterogeneity of DiGeorge syndrome. The criteria for velocardiofacial syndrome are DiGeorge cases which are more severely deleted than the expansive phenotype of velocardiofacial syndrome so that the diagnostic label is more easily attached. Even so, 17% of Driscoll's DiGeorge cases were not deleted at 22q11. It may be that the 83% prevalence of deletions denote that the majority of DiGeorge cases actually are caused by the deletion specific to velocardiofacial syndrome. Stated another way, the 17% of DiGeorge cases not deleted may be related to some of the other chromosomal sites to which DiGeorge has been linked (such as 4q, 10p, and 17p, among others) whereas, to date, velocardiofacial syndrome has been isolated only to 22q11.

Finally, Dr Hall's support of the new acronym CATCH 22 only serves to confuse the clinical and diagnostic picture further. Dr Hall cites Driscoll's prevalence data as if to indicate that velocardiofacial syndrome is aetologically heterogeneous. She states that... 68% of Shprintzen's velocardiofacial patients... have been recognised to have deletions of 22q11. This statement is not true. It should more accurately be stated that 68% of patients sent to Dr Scambler's laboratory identified by other clinicians as having velocardiofacial syndrome were deleted. In our sample, 100% were deleted. Is this a difference in clinical experience, expertise, criteria, or all of the above? There is simply no valid evidence to suggest that velocardiofacial syndrome is aetologically heterogeneous. The DiGeorge anomaly is known to be so, as is CHARGE. Therefore, placing velocardiofacial syndrome, DiGeorge syndrome, and CHARGE under a single diagnostic category is an example of what used to be referred to as "jumping", which will only confuse clinicians, molecular geneticists, and, most importantly, patients and their families. If the data reported in volumes 30 (pages 801-856) point out nothing else, it is that molecular geneticists are dependent on accurate clinical detection in order to prove primary aetiology.

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Multiple origins of X chromosome tetrasomy

The extra chromosomes in all previously reported cases of X chromosome tetrasomy or pentasomy have been maternally derived and compatible with being the product of successive meiosis I and meiosis II nondisjunctions in the mother. This is inferred by the presence of heteromethylation for maternal alleles at all informative X loci, implicating transmission of one or both chromosomes from both X chromosome pairs from the mother. In our investigation of 22q11.2 deletions, maternal origin, molecular results for one 46,XXXX case were incompatible with a completely meiotic origin of the extra chromosomes. However, other informative cases of maternal extra chromosome reports in that there was complete absence of any paternal alleles.