Autosomal dominant simple microphthalmos: incomplete penetrance and variable expression in a large family

We read with interest the well documented report by Vingolo et al on "Autosomal dominant simple microphthalmos". The authors describe a large pedigree with 14 persons in four generations affected with bilateral microphthalmos without other ocular or systemic signs. The family data were most compatible with autosomal dominant inheritance with complete penetrance. Based on the findings in this family and a review of published reports the authors concluded that "simple, partial, posterior pure microphthalmos and nanophthalmos are similar clinical entities sharing total axial length and vitreous cavity length reduction".

During the past few years we have been contacted by several members of a large family (see pedigree in the figure) for genetic counselling after the birth in this family of three children (II-6, III-7, IV-1), two boys and one girl, with "uncomplicated" bilateral anophthalmos. All three are mentally normal at the respective ages of 12, 9, and 8 years.

Further clinical and laboratory examinations, including chromosome studies, were normal but CT scans of the brain showed complete absence of occular structures but normal optic nerves in all three. Further familial investigation showed normal ophthalmological findings in all family members, except I-1 (paternal great grandfather of V-1) and maternal grandfather of III-6 and III-7 (paternal grandfather of IV-1) and III-4. All three presented a unilateral left sided extreme form of microphthalmos with cloudy cornea and total axial lengths below 8 mm. Clinical and biometric findings of the contralateral eyes were normal.

The ocular anomalies in the affected members of the present family thus varied greatly from bilateral true anophthalmos to unilateral microphthalmos with small anterior segment and cloudy cornea. The findings in this family are most compatible with autosomal dominant inheritance with variable expression and incomplete penetrance and confirm the observations reported by Bateman who described a three generation family with non-colobomatous microphthalmos dominantly inherited with incomplete penetrance and variable expressivity.

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Grebe syndrome: a very severely affected case

Grebe syndrome is a very rare form of short limb dwarfism, inherited as an autosomal recessive trait. It is characterised by shortening affecting the lower limbs more than the upper limbs and distal parts more than proximal parts resulting in bulbous fingers and toes, whereas the head, neck, and trunk are essentially normal. The classical clinical and radiological features and other unusual clinical features have been described previously. In the present communication we report an extreme form of Grebe syndrome in which there was a total absence of bones in the lower limbs, features which have not been reported previously.

A male neonate was born at term to a consanguineous couple (uncle-niece) showing characteristic features of Grebe chondrodysplasia (fig 1). There was progressive shortening of the limb bones from the proximal to distal ends. The lower limbs were more severely affected than the upper limbs. The hands and feet were extremely small with bulbous digits. There were four fingers and a thumb on both hands and five toes on both feet. The head, neck, and trunk were essentially normal. His length was 30 cm, upper segment 24 cm, lower segment 6 cm, head circumference 30 cm, chest circumference 27 cm, upper limb length 10-5 cm, lower limb length 8 cm, and weight...

Figure 1 Infant with Grebe syndrome.

Figure 2 Whole body radiograph of the infant.
1700 g. Systemic examination did not show any abnormality and neonatal reflexes were normal.

A radiograph showed the following radiological abnormalities (fig 2). In the upper limbs, there were short humeri, short, thick, bowed radii, absence of the ulna on the left and a rudimentary ulna on the right (speck of calcification), and absence of the carpal bones and phalanges. In the lower limbs there was total absence of all the bones. The chest was bell shaped and the skull, spine, and pelvis were normal. Skeletal survey of both parents showed no abnormalities.

An x ray of the lower limbs taken at 3 months of age (fig 3) showed total absence of bones in the lower limbs. This later x ray was taken to confirm our assertion that it was aplasia rather than delayed ossification.

Though the inheritance of this disorder has been considered to be autosomal recessive, the data suggest that the gene may have some effect on heterozygotes. The abnormalities reported in heterozygotes include absent phalanges, anatomical changes of the phalanges, talipes equinovarus, polydactyly, and double halluxes. Neither of the parents of our case showed any abnormalities. The characteristic shortening noted in Grebe syndrome includes more severe involvement of the lower than the upper limbs and progressively increasing shortening from proximal to distal portions of the limb. The absence of the ulna and the phalanges is characteristic of Grebe syndrome. However, we are not aware of any case of Grebe syndrome with total absence of the bones in the lower limbs, as reported in the present case. When the gene for Grebe syndrome is expressed fully, it may result in total failure of bone formation.


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Twins as a Tool of Behavioral Genetics

This book is based on a Dahlem workshop which was held in 1992. The book consists of our sections on the ability of intelligence, personality, psychopathology in childhood, and adult psychopathology. Each section includes a series of background papers written by international experts and a group report from the workshop participants.

This is an excellent book which would be of interest to those involved in behavioural twin research. It would also be useful to those who are searching for ideas for future work. The chapters and discussions are particularly interesting as they focus on potential difficulties with twin studies, current thoughts, and ideas for future research rather than simply reviewing published findings. The main drawback is that although most chapters are well written, the contributions vary markedly in quality. Also some group reports may appear somewhat disjointed if they are not read in conjunction with the accompanying background papers.

In the first section on cognitive abilities, the question of how intelligence should be defined and the importance of a general ability factor is debated. The discussion focuses on the use of twin studies to design measures of intelligence and the incorporation of multivariate analyses to explore the covariation among abilities. The importance of longitudinal studies to investigate developmental mechanisms and the role of twin studies in identifying environmental influences are also highlighted.

The papers on personality cover the issue of how personality can be defined with particular reference to the five factor model. Translational psychology of personality is considered and once again the importance of longitudinal studies is highlighted. The participants also emphasise the need for direct assessments of environmental factors and note that there has been insufficient research on the relationship between normal personality and psychopathology.

In the section of childhood psychopathology, the need for genetic research in this age group is highlighted. Most of the issues discussed are, however, relevant for all age groups. The comparability of twin studies and potential sources of bias in twin studies are covered in some detail. The potential uses of twin studies, for example, in defining phenotypes and investigating comorbidity, are discussed and the issue of measurement is also raised.

The papers on adult psychopathology also highlight the difficulties in making valid diagnoses and point out the merits of twin studies in refining phenotypes. The group again highlight the role of discordant MZ twins in studying the contribution of environmental factors and the pathophysiology of disorders and the importance of twin studies is illustrated by findings for alcoholism.

Overall there are some general issues which emerge from all the groups. The importance of the assumptions of the twin method are repeatedly considered. The value of longitudinal studies and the importance of direct measures of environment are also highlighted. It is acknowledged that twin studies are particularly useful in defining phenotypes and finally there is a general agreement that the advent of molecular genetics research does not portend that there is no longer a place for twin research. It appears that there is still a need for twin studies which provide a different yet often complementary approach to molecular methods.

ANITA THAPAR


Clinical geneticists are often confronted by clients and are faced with, or have a family history of, an untreatable inherited neurological disorder and these people are well aware of the limitations of currently available therapy. They are often members of lay support associations and through their newsletters take particular interest in new therapeutic strategies targeting the relevant disorder. Indeed they are often aware of such strategies before their medical practitioners and can pose challenging questions at interview/counselling sessions.

Intracranial transplantation of tissues to alleviate the symptoms of neurological degeneration has a long history in experimental neurobiology. The editors of this impressive volume trace the first publication on the subject to 1890. In the 1980s this strategy was applied for the first time to humans: autologous adrenal medulla was grafted into the caudate or putamen of people with advanced Parkinson's disease (PD). The results varied but the public attention has been caught; neural transplantation was in the public arena. The questions coming from patients were addressed to neurologists and, as the vast majority of cases of PD are not inherited, clinical geneticists escaped. The early studies of adrenal transplantation have been superseded by those using human embryonic mesencephalic tissue and few would now doubt the relative success of this strategy in alleviating the symptoms of advanced PD. This success has resulted in the proponents of neural transplantation widening the scope of the diseases to be targeted. Huntington's disease is now firmly on the agenda and indeed some transplantation has already been carried out and reported in abstract form. The first pan-European programme for recruitment towards transplantation of embryonic striatum into HD patients has already been established and the topic is discussed by members of the lay associations for HD. So, where does the practising geneticist turn to

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