

"CATCH 22" sans cardiac anomaly, thymic hypoplasia, cleft palate, and hypocalcaemia: cAtch 22. A common result of 22q11 deficiency?

The recent invited Editorial and outstanding series of articles in this Journal¹⁻⁸ describe 22q11 deletion with the acronym "CATCH 22" (Cardiac anomaly, Abnormal facies, Thymic hypoplasia, Cleft palate, and Hypocalcaemia). Although the phenotypic variability was noted, it should be emphasised that many patients present with extremely mild symptoms and do not recapitulate the full spectrum alluded to by the "CATCH 22" acronym. Thus, the unifying feature appears to be the presence of a 22q microdeletion. Of a cohort of 150 presumed "CATCH 22" cases followed in Australia, only 35% have a significant cardiovascular anomaly and 25% overt or submucous cleft of the palate. Only 10 have the complete DiGeorge syndrome or a "full CATCH". To illustrate the milder range which constitutes the majority of the Australian patients, we wish to report a case of 22q11 deficiency that did not have Cardiac anomaly, Thymic hypoplasia, Cleft palate, or Hypocalcaemia.



The proband.

The proband was referred from a developmental assessment unit at the age of 11 because of hypernasal speech. Her parents are normal, white, and unrelated, and in their mid thirties. She has one sib, a female, two years older, who is normal. The pregnancy was uneventful and she was born at 37 weeks weighing 2340 g with a length of 48.8 cm. Her early development was slightly slow but not outside normal limits. She smiled at 12 weeks, sat at 8 months, crawled at 10½ months, and walked at 15 months. She started to join words together by about 2½ years of age. Ear infections started at 8 to 9 months. Glue ear was diagnosed and ventilating tubes were inserted for the first time at the age of 2 years. Feeding and swallowing have been unremarkable, though she occasionally regurgitated milk through the nose. An umbilical hernia was repaired at the age of 2½ years. She is in mainstream schooling, but has needed remedial teaching. Teachers report an enthusiastic and cooperative girl who is having great difficulty with mathematics and any subject which requires logic and reasoning. When tested on Stanford Binet IQ scale 4th edition, she functioned in the borderline to low average range.

On examination, at 11 years of age, her height was between the 10th and 25th centiles, weight between the 10th and 25th centiles, and head circumference between the 50th and 75th centiles. She had a "long" face, deficient alaeque, almond shaped palpebral fissures, dysplastic ears with inturned edges, and a small lower jaw (figure). There was no hypotonia. Serum calcium and parathyroid hormone were normal. Formal cardiac assessment and echo showed no abnormality, including the conotruncal region, such as right aortic arch. Immunological testing including T cell subsets, Concanavalon A, and T cell esterase were within normal limits. Her palate appeared short and she had hypernasal speech. Her speech was intelligible but the parents reported that often people ask her to repeat what she has said and her speech deteriorates when she is tired. Videofluoroscopy showed a good movement of the palate with a good knee to the palate; hearing was normal. Pharyngoplasty and palatal lengthening resulted in reduction of hypernasality and increased intelligibility.

High resolution chromosome analysis to the 700 band level was normal. FISH analysis was performed using a cosmid probe corresponding to locus D22S75 (N25) within the DiGeorge critical region. A distal marker, Cos82, was used as a control probe to identify the chromosome 22 homologues. A hybridisation signal was detected on only one of the chromosomes 22 in 15/15 metaphases examined with marker N25. This finding is consistent with the presence of 22q11 deletion.

Although this patient may represent one end of a spectrum, the absence of overt or submucous cleft palate, overt or subclinical conotruncal congenital heart disease, hypoparathyroidism, or thymic deficiency was not unusual in our 22q11 deleted patients. For the patient we describe here, the thymus may have failed to descend completely, but it is clearly functional.⁹ Further, it is clear that the size of the deletion does not appear to determine or correlate with the severity of the anomalies.¹⁰ Thus, ascertainment of mild cases in parents and their offspring is important for proper genetic counselling, as intrafamilial variability is common.⁶ This is an important syndrome for the dysmorphologist to recognise¹¹ and, though con-

sciousness can be increased by the acronym "CATCH 22" it should not be rigidly adhered to in establishing a provisional diagnosis of 22q deletion.

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Skeletal malformations and polycystic kidney disease

Dr Winter's comment¹ on our paper describing an infant with autosomal dominant polycystic kidney disease (ADPKD) and skeletal malformations² raises an interesting point as to the possible diagnostic framing of the complex polysyndactyly present in the patient. We are grateful for the opportunity to discuss this case further and to give more clinical and radiological details, as suggested.

Our patient had complete bilateral syndactyly of the hands associated with forced flexion and soft tissue fusion. Radiographs showed five metacarpals, hypoplastic

thumbs, and an unspecified number of partially overlapping phalanges, without bone fusion. A triphalangeal thumb was present on at least one side. The feet showed seven digit polysyndactyly with absent talus. Fibular diaphyses appeared angulated. The knees were dislocated.

Only some of these features are consistent with Haas type IV polysyndactyly,³ which appears to be inherited as an autosomal dominant trait (MIM 186200⁴). However, the radiographic pattern of the hands and feet of the patient's parents were normal, and none of the relatives showed hand or foot abnormalities. Assuming that a single gene defect is responsible for the observed complex phenotype, either a de novo dominant mutation or recessive transmission might be suggested.

Diagnostic evaluation, kindly performed by Professor R S Lachman of the International Skeletal Dysplasia Registry at UCLA, showed that the radiological findings in our case were most compatible with mesomelic dysplasia - Werner type,⁵ but with some major atypical clinical and radiographic features, most similar to some variant cases reported by Kozłowski and Eklöf.⁶ Complete syndactyly is not a feature of Werner type mesomelia.

There have been several reports of polydactyly/syndactyly associated with hypoplastic/absent tibiae. All were dominantly transmitted. A newborn girl with type IV syndactyly and bilateral hexadactyly of the hands and feet has been reported with unilateral absence of the tibia,⁷ and another girl with partial tibial aplasia associated with syndactyly has been described.⁸ Al-Awadi *et al*⁹ described a large four generation Arab family in which as many as 17 members had bilateral syndactyly or polydactyly or both. The proband also had hypoplastic bowed tibiae. Lamb *et al*¹⁰ described 15 members in a five generation kindred with five fingered hands associated with preaxial polydactyly of the fingers or toes and partial or complete absence of the tibiae. Yujnovsky *et al*¹¹ reported polydactyly/syndactyly, triphalangeal thumbs, and tibial hypoplasia in four members in three generations.

We are not aware of any cases of Werner mesomelic dysplasia or of Haas type IV polydactyly associated with polycystic kidney disease.

Interestingly, Cameron¹² described an adult female with bilateral polycystic kidney disease associated with bilateral teratodactyly of the feet (split and cloven feet with a "lobster claw" appearance) and bilateral hand deformities with triphalangeal thumbs, with normal tibiae. The disorder appeared to be transmitted in a dominant fashion. The possibility was raised that congenital abnormalities of the kidneys and of the extremities might occur more often than at random.¹²

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NOTICES

Lilly Colloquiums 94

Every year, the Lilly Institute, France, for the development of medical knowledge, in collaboration with the recipients of the Lilly International Research and Study scholarship, organises the Lilly colloquiums. They will be held this year on Thursday 13 October 1994 at Palais des Congrès, Salle 62 AB, 2 Place de la Porte Maillot, 75017, Paris, France. The subject will be 'Genetics and Cancer' with the following speakers: P Tambourin (Paris), H T Lynch (Omaha), G Thomas (Paris), P May (Villejuif), E Solomon (London), J Rowley (Chicago), R Berger (Paris), J Jouanneau (Paris), A Dejean (Paris), and A Kahn (Paris). For further information contact M H Sadorge, tel: 49.11.34.39.

Genetics in Europe Now

A *Nature* one-day conference on "Genetics in Europe Now", a debate on European policies on genetics, as part of its 125th anniversary celebrations will be held at Brandenburg Akademie, Berlin, on 30 September 1994. Fee: DM195/£75. Languages of the conference: German and English. For further information please contact: Christine Jones, Conference Organiser, *Nature*, 4 Little Essex Street, London WC2R 3LF, UK. Tel: +44 71 836 8833 x 2593. Fax: +44 71 379 5417.