**LETTERS TO THE EDITOR**

Kenny-Caffey syndrome without the CATCH 22 deletion

With regard to the recent report by Sabry et al., we would like to present an additional case of Kenny-Caffey syndrome who, unlike their case, did not have a chromosomal deletion at 22q11.2 (the CATCH 22 region). We also report detailed test results for calcium metabolism and response to combination therapy with vitamin D, magnesium, and growth hormone.

The female patient was born after 40 weeks of an uneventful pregnancy to non-consanguineous, healthy, Japanese parents. She weighed 2750 g and measured 46 cm at birth. At 1 month, she had an episode of generalised convulsions because of hypocalcaemia. During this episode, her serum calcium, phosphorus, magnesium, and intact PTH were 5.0 mg/dl (reference range 8.6-9.7), 9.1 mg/dl (2.7-4.3), 1.2 mg/dl (1.8-2.2), 120 pg/ml (94-156), and 15 pg/ml (15-50), respectively. Oral 1α-vitamin D (0.3 μg/day) was started on the basis of a diagnosis of hypophosphata mia. The patient's serum calcium levels were normalised although her intact PTH remained at low to non-normal levels. She had another episode of hypocalcaemic convulsions at 9 months of age. At the age of 5 years 1 month, she was referred to our hospital for further examination.

Physical examination showed her to be of proportionally short stature. Her height was 84.2 cm (mean −5.3 SD) and her weight was 12.2 kg. She had normal intelligence, a prominent forehead, and slender extremities. Her anterior fontanelle still showed an opening of 1 x 1 cm. She had severe hyperopia with normal optic fundi. Radiological examination showed medullary stenosis of the long bones typical of Kenny-Caffey syndrome. CT scan of the brain showed fine calcification in the basal ganglia. Although her serum calcium remained normal with relatively low doses of vitamin D, the EDTA loading test (50 mg/kg) indicated a blunted response for i-PTH (basal 12.8 pg/ml, peak 17.5 pg/ml). The PTH loading test showed a normal response to exogenous PTH with increased urinary excretion of phosphorus and cAMP. Growth hormone provocative tests showed normal response.

As in the case of Sabry et al., we also suspected the possibility of the patient having a deletion in the CATCH 22 region. However, FISH analysis on peripheral blood lymphocytes (probe D22S75, and inl) showed a normal diploid state. The patient was then put on a combination therapy of vitamin D (1 μg/day) and magnesium sulphate (0.4 g/day). Since her short stature did not improve with this therapy, growth hormone therapy (0.5 IU/kg/week) was initiated at the age of 7 years 5 months. After two years of this therapy, the height standard deviation for her chronological age improved from −5.4 SD to −4.4 SD without appreciable acceleration of bone maturation.

The reason for the discrepancy between the Bedouin family reported by Sabry et al. and our case remains unclear. One possibility is that the genetic heterogeneity of the syndrome. Of the 47 reported cases, more than half were familial and both autosomal dominant and recessive forms have been reported. 1-2 The cases reported by Sabry et al. had interesting and unusual features for the syndrome, such as microcephaly, microcephaly, and severe mental retardation, while our case had more typical features of the syndrome. Most of the Bedouin cases of the syndrome show mental retardation, 1 while this is rare in other populations. It is therefore possible that the syndrome in Bedouins is genetically different from that in other ethnic groups. Another possibility is that the gene is actually in the CATCH 22 region but the defect varies from large scale deletion to subtle mutations. It is also possible that the different phenotypes are caused by a contiguous gene effect. Without a large scale deletion, the phenotype would be more typical of the syndrome.

Finally, a combination therapy of vitamin D, magnesium, and growth hormone seems to be moderately effective in the treatment of intermittent symptoms without increasing the risk of hypocalcaemic attacks. More efforts should therefore be made to improve the final height of these patients.

TOHRU YORIFUJI
JUNKO MURAI
AYUMI UEMATSU
Department of Paediatrics, Kyoto University Hospital, 54 Shogoin Sakyo, Kyoto 606-8507, Japan


Kenny-Caffey syndrome is part of the CATCH 22 haploinsufficiency cluster

The paper by Sabry et al. described four affected sibs with Kenny-Caffey syndrome, and on the basis of the cytogenetic findings the authors postulated that this disorder is part of the CATCH 22 haploinsufficiency cluster. They did, however, comment that the clinical features in these patients are different from those previously described in Kenny-Caffey syndrome.

Phenotypically these patients are much more like those described by Richardson and myself in 1990, 1 with a number of subsequent reports of similar children. These children have all been of MIDDLE EASTERN origin and do appear to represent a separate entity from Kenny-Caffey syndrome.

JEREMY KIRK
Department of Gynecology and Endocrinology, Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH, UK


Genotypic/phenotypic heterogeneity of Kenny-Caffey syndrome

Several reports have accumulated delineating Kenny-Caffey syndrome (KCS) in presumed

**Kenny-Caffey syndrome is part of the CATCH 22 haploinsufficiency cluster**

Kenny-Caffey syndrome reported an interesting Bedouin sibship with Kenny-Caffey syndrome. The two surviving children and their mother were found to have a microdeletion of the region commonly deleted in the CATCH 22 spectrum of phenotypes. On further investigation, it was shown to be inherited from their phenotypically normal mother. The authors concluded that their observation widens the phenotypic spectrum of CATCH 22 to include the features of Kenny-Caffey syndrome, namely severe growth retardation and cortical thickening/medullary stenosis of the tubular long bones. However, Khan et al. reported six Bedouin sibships all with paren-
monogenic dominant (OMIM 127000) and recessive (OMIM 244460) forms. In the previously reported family, we recently ascertained some more patients in unrelated Bedouin families, who met the criteria for the diagnosis of KCS and had the same traits (microcephaly and psychomotor retardation), with the consensus of phenotype in Arab children from the classic profile of KCS. In one particular new, non-consanguineous, Bedouin family, a brother, who died at the age of 6 months, had the DiGeorge syndrome (DGS) with major cardiovascular involvement, while his older sister had the Arab phenotype of KCS, without any cardiovascular manifestations. Cardiovascular involvement reemphasises the chromosome 22ql 1 fraction, but has not been emphasised as a major component of the KCS profile. Thus, within this particular family, a clinical link between Kenny-Caffey syndrome and DiGeorge syndrome was established by the coexistence of the two phenotypes in the same sibship. Moreover, a paternally inherited 22q11 microdeletion was also identified in this new family, a further support, in addition to the clinical link, for a molecular link between KCS and DGS. 1,2

The identification of 22q11 microdeletion in only a fraction of patients with KCS is not surprising, since 22q11 microdeletions can also be found in some Bedouin patients with the Arab phenotype of KCS has been previously reported and has also been our experience in some of our recently ascertained families. Genetic heterogeneity seems to be evident in KCS, as it is in DGS, certainly with room for other possibilities in addition to monosomy 22q11. Because of the clinical overlap between KCS and DGS, it would be reasonable to explore the possibility that, like DGS, some patients with KCS might have some abnormality of chromosome 10p. There is also potential for the possibility of monogenic inheritance, although it is our opinion that the comparison between KCS and Bedouin Souter syndrome is probably less valid than one may think. It seems more likely that KCS is a contiguous gene syndrome, as is probably the case for DGS, rather than being the result of one or more genes to be located in the small 22q11, as in the case of Bernard Souter syndrome. Also, one additional mechanism that could account for the inter-intrafamilial phenotypic heterogeneity of KCS is the interaction of several individual background genes that would be expected to modify the phenotype.

Although the report by Khan et al, also from Kuwait, 3 comments on the notion of autosomal recessive inheritance for the Arab variant of KCS, none of the families mentioned in this report was investigated for potential 22q11 hemizygosity. In that report, the presence of consanguinity, and several affected family members of both sexes, has been used to point to autosomal recessive inheritance as the mode of inheritance in Bedouin families. It is recognised that the presence of consanguinity and multiple affected members in the same sibship would “suggest” autosomal recessive inheritance. On the other hand, the same criteria should not be seen as evidence that “confirms” autosomal recessive inheritance, as the paper by Khan et al,4 emphatically stated, even in the title. In Kuwait, with consanguinity occurring in the traditional marriages, one would expect an excess of recessively transmitted diseases. By the same token, the widespread parental consanguinity among Bedouins tends to reduce the importance of this parameter in the analysis of the mode of inheritance.

Presumably, the presence of some peculiar traits in Arab patients, microcephaly and psychomotor retardation, has caused some confusion in the diagnosis of such cases. To that effect, reports of some Arab children with the phenotype described above 1 have been lumped into an isolated category (OMIM 244110) that has been designated “Sanjad-Sakati syndrome” in the McKusick catalogue, after the authors who first reported this phenotype in Saudi Arabia. Surprisingly, the Bedouin patients recently reported by Khan et al 2 have been listed in this as part of the proposed autosomal recessive entry of Kenny-Caffey syndrome, despite the fact that they have the same “Arab phenotype.”

We have been prompted to review medical publications for cases with the phenotype mentioned above in an attempt to determine whether they represent a separate syndrome or an Arab variant of KCS. The details of this review are described elsewhere. Our results indicate that the main features of the Arab phenotype are very similar, if not identical, to the KCS phenotype. At least in part, the presence of microcephaly in Arab patients is probably apparent, considering the global reduction that the anthropometric indices consequent upon their severe postnatal developmental retardation. While medullary stenosis of the long bones seems to be the most consistent finding in KCS, it is only seen in a smaller fraction of Arab cases. However, this number may be an underestimate since in some of the reports describing this Arab phenotype, there was no mention of any radiological assessment to verify the presence or absence of medullary stenosis. Finally, there are some different possible alternative mechanisms to explain the association of the Arab variant of KCS with some peculiar traits. One attractive possibility, for example, is the interaction with certain background ethnic specific mutations.

Again, we would like to re-emphasise the coexistence of both DGS and Kenny-Caffey syndrome (OMIM 127000) in the same sibship, as described previously, which indicates that these syndromes should be seen as a spectrum of a host of traits rather than being rigidly classified into separate entities. In conclusion, the evidence for association of the genotypic/phenotypic heterogeneity encountered in KCS and its Arab variant, more thorough effort is needed through a world wide collaboration between different centres.

M A SABRY
M ZAKI
A SHALOUT
Kansai Medical Genetic Centre and Paediatric Department, Fukuwa Kansai, Japan

References

Tricuspid atresia in sibs

Tricuspid atresia is a rare cardiovascular malformation (CVM) and familial recurrence is uncommon. In the Baltimore-Washington Infant Study (BWIS), 1 one girl (of 93 probands) with tricuspid atresia had a sister with an unspecified CVM. Weigel et al 2 reviewed the occurrence of heart defects in 210 sibs of 96 probands with tricuspid atresia. One boy had an older sister with atrial septal defect (not specified whether secundum or primum type) and another older sister had mitral valve prolapse. Grant 3 described a boy with the coexistence of tricuspid atresia with pulmonary stenosis whose younger sister had Ebstein anomaly. We report the first instance of tricuspid atresia in sibs.

The proband, an Italian boy, was diagnosed with hypoplastic left heart syndrome and catheterisation with classical tricuspid atresia. He had leovcardia with situs solitus of the atria and viscers, right atriopenicular valve atresia, D ventricular loop, and normally related great arteries. At the age of 7 months, he had surgery for a right atrial-pulmonary artery Fontan anaostomosis, but died shortly afterwards of heart failure.

The younger brother, now 7 years old, was born eight years later to the same parents. He had the same cardiac anatomy as his brother and was treated with a Glenn superior vena cava-pulmonary artery shunt. He is currently a candidate for a Fontan-type anastomosis.

Neither boy had dysmorphic facial features or non-cardiac malformations. High resolution prometaphase (1250 bands) chromosome analysis was normal in both (46,XY). Fluorescent in situ hybridisation was negative for chromosome 22q11 microdeletion. The family history is negative for cardiovascular malformations. The parents are not related. Auscultation of them was normal; echocardiogram and electrocardiogram were refused. The maternal prenatal history was negative for exposures.

The recurrence risk for sibs with tricuspid atresia is low, about 1.0%. 1,4 The family in this report typifies the challenge of providing accurate genetic counselling for many families with non-syndromic CVMs. Assuming the parents are not affected, the suggested risk of recurrence after two affected sibs tripled to 3%.

The occurrence of tricuspid atresia in two brothers may tempt one to speculate that autosomal or X linked recessive inheritance is present, implying a much higher risk of recurrence. Further evidence for an X linked gene is suggested by the significant odds ratio for males with tricuspid atresia (1.93) in the BWIS, which follows in frequency the more familiar male predominance of d-transposition of the great arteries (2.57) and VSD of 5. 5 The parents have not had echocardiography to determine if they have a clinically asymptomatic microform of tricuspid atresia, which would implicate maternal transmission. As our understanding of the genetic factors causing CVMs increases, so may our ability to counsel specifically rather than using empirical data only.

1. ANGELO E LIN
Genetics and Teleradiology, Centro Genetico Infantil, Centro Hospitalar Universitario de Sao Paulo, Brazil
2. LUCA ROSTI
Cattedra Cardiologica, "C " (Milano), Ospedale Clinico San Donato, Via Morandi 30, 20097 San Donato Milanese, Milan, Italy)
Genotypic/phenotypic heterogeneity of Kenny-Caffey syndrome.

M A Sabry, M Zaki and A Shaltout

doi: 10.1136/jmg.35.12.1054-c

Updated information and services can be found at:
http://jmg.bmj.com/content/35/12/1054.4.citation

These include:

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/