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 275 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/kg/day) was started on the basis of a diagnosis of hypopharythropathyroidism. The patient’s serum calcium levels were normalised although her intact PTH remained at low to low-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 fontanella 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 to the test.

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 using probe D22S74 and int3 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. The cases reported by Sabry et al. had interesting and unusual features for the syndrome, such as marked IUGR, 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, 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 intact PTH levels in patients without increasing the risk of hypocalcaemic attacks. More efforts should therefore be made to improve the final height of these patients.

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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 of previously described in Kenny-Caffey syndrome.

Phenotypically these patients are much more like those described by Richardson and myself in 1990, 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.

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

Kenny-Caffey syndrome includes the following features: (1) 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 this was shown to be inherited from the mother phenotypically normal mother. The authors concluded that their observation widens the phenotypic spectrum of CATCH 22 to include this deletion. (2) The second feature is severe growth retardation and cortical thickening/medullary stenosis of the tubular long bones. However, Khan et al. reported six cases in which Kenny-Caffey syndrome was not associated with features of the disorder, suggesting that Kenny-Caffey syndrome is an autosomal recessive trait. There are at least two other possible explanations for the findings in Durenberg-Soulier syndrome. The first is that the children have autosomal recessive Kenny-Caffey syndrome in keeping with this being a consanguineous family with the chromosomal deletion being a second, independent abnormality. The other possibility is that the mutations have been caused by a separate mutation in the Durenberg-Soulier syndrome. This hypothesis could easily be tested in the consanguineous Bedouin sibships reported.

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Genotypic/phenotypic heterogeneity of Kenny-Caffey syndrome

Several reports have accumulated delineating Kenny-Caffey syndrome (KCS) in presumed consanguinity, with a total of 16 children with features of the disorder, suggesting that Kenny-Caffey syndrome is an autosomal recessive trait. There are at least two other possible explanations for the findings in the family described by Sabry et al. The first is that the children have autosomal recessive Kenny-Caffey syndrome in keeping with this being a consanguineous family with the chromosomal deletion being a second, independent abnormality. The other possibility is that the mutations have been caused by a separate mutation in the Durenberg-Soulier syndrome. This hypothesis could easily be tested in the consanguineous Bedouin sibships reported.
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, along with distinctive craniofacial abnormalities) in Arab children from the classical profile of KCS. In one particular new, non-consanguineous, Bedouin family, a brother, who died at the age of 6 months, had the features of the DiGeorge syndrome (DGS) with major cardiovascular involvement, while his older sister had the Arab phenotype of KCS, without any cardiovascular manifestations. Cardiovascular involvement re-emphasises the role of interactions with individual background genes that would be expected to modify the phenotype.

The report by Khan et al., also from Kuwait, promotes the notion of autosomal recessive inheritance for the Arab variant of KCS, none of the families mentioned in this report was investigated for potential 22ql1 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 arthritis. 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. emphatically stated, even in the title. In Kuwait, with consanguinity occurring in 80% of all 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 diagnostic criteria of such cases. To that effect, reports of some Arab children with the phenotype described above have been lumped into an isolated category (OMIM 241140) that has been designated "Saud-Sabri syndrome" in the Mendelian catalog, 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 category as part of the phenotypic spectrum of Kaffey-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. 3 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 in brain size and the lowering of the midline indicator consequent upon their severe pre-/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 the 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 (or its Arab variant) in the same sibship, as described previously, 4 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, for the evaluation 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.

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), one girl (of 93 probands) with tricuspid atresia had a sister with an unspecified CVM. Weigel et al. 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 et al. described a boy with the syndrome of tricuspid atresia and 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 patent ductus arteriosis and catheterisation with clinical tricuspid atresia. He had levocardioc with situs solitus of the atria and viscer, right atrioventricular valve atresia, D ventricular loop, and normally related great arteries. At 5 months of age, he had surgery for a right atrial-pulmonary artery Fontan anomaly, but died shortly after wards 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%. 1,5 The family in this report typifies the challenges 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 triples to 3%. 5

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 of X-linked dominant inheritance (2.52). 5 The parents have not had echocardiography to determine if they have a clinically asymptomatic microform of tricuspid atresia, which would indicate X linked dominant inheritance. As our understanding of the genetic factors causing CVMs increases, so may our ability to counsel specifically rather than using empirical data only.

References
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