LETTERS TO THE EDITOR

The SNATIATION reflex

I read with the greatest delight the report by Teebi and Al-Saleh describing (possibly one of their own families in keeping with the ACHOO tradition) the autosomal dominant inheritance of a sneezing disorder provoked by fullness of the stomach.

As the authors point out (possibly with tongue in cheek) it may not be all that uncommon a condition, but simply has not been previously reported because it does not lead to major disability. On the other hand it could be socially embarrassing or even stigmatising, albeit highly preferable to a compulsive belching reflex at the end of heavy meals.

The basic epidemiological and genetic questions of frequency, prevalence, selective advantage, presence in other species, pathogenic mechanism, linkage, nucleotide sequence, number of introns (perhaps related to the number of sneezes), transposable elements, etc await further investigation. However, I would like to suggest that a catchy acronym may hasten the process of reporting other families (although it hasn’t helped ACHOO much). Therefore, I propose the newly described condition be called the SNATIATION reflex—a combination of sneezing and satiation and easily remembered by the acronymic handle of Sneezing Non-controllably At a Time of Indulgence of the Appetite—a Trait Inherited and Ordained to be Named.

In all seriousness I really was delighted to see the report, both because it tickled my imagination and because I think it is important to report ‘normal’ traits both structural and behavioural. We tend to teach human genetics by diseases and have few examples of non-pathological traits determined by single genes. Furthermore, the mechanisms involved in producing the sneezes in both the ACHOO and SNATIATION reflexes are totally unknown. Are there other inherited sneezing reflexes? Time to get busy surveying friends, relatives, and clinic personnel!

JUDITH G HALL
University of British Columbia Clinical Genetics Unit, Grace Hospital, Vancouver, Canada.


Angelman’s syndrome

It has taken dysmorphologists a number of years confidently to recognise the facial features of the syndrome characterised by severe mental retardation, marked speech impairment (usually less than three words), jerky movements, and a happy disposition. Angelman’s syndrome is now well established as a clinical entity with a recognisable facial appearance, a distinctive EEG pattern, and a chromosomal deletion of 15q11-13 in 40 to 50% of cases. Indeed it is often possible to suggest the diagnosis from facial photographs.

We wish to draw attention to an error that we have made on two occasions in the past few years which will be of interest to clinicians. Angelman’s syndrome was originally thought to be the diagnosis in the two girls we describe at about 2 years of age. With time the diagnosis of Rett’s syndrome became obvious. Both patients have a similar facial appearance with the subtle facial dysmorphism seen in Angelman’s syndrome, that is, a prominent lower jaw, a wide mouth, and midfacial hypoplasia. The two patients who were erroneously diagnosed as having Angelman’s syndrome at about 2 years of age both tended to tongue thrust, had jerky movements, seizures, and significant global delay with minimal speech. As time went on, regression became apparent with deceleration in the rate of head growth leading to microcephaly; they lost their happy disposition and developed the typical involuntary hand stereotypies of Rett’s syndrome. The similar facial dysmorphism of Angelman’s and Rett’s syndromes may be more readily confused in a girl with Rett’s syndrome who has early developmental delay, contrasting with the classical description of Rett’s syndrome with normal early development.

We advise caution in making the diagnosis of Angelman’s syndrome in girls at about 2 years of age without the commonly associated EEG features and with normal chromosomes. The recurrence risk in Angelman’s syndrome with no chromosomal abnormality may be 25% in contrast with Rett’s syndrome which carries a low recurrence risk.

(a) (b)

Figure 1 Case 1 (a) aged 2 years, (b) aged 4 years.
Case report 1 (fig 1)
This girl, who was first seen at 20 months, was the second child of unrelated Caucasian parents. Their first child was born prematurely and died in the neonatal period. Our patient was delivered at term by elective caesarean section after an uncomplicated pregnancy, weighing 3100 g. She smiled at 6 weeks but was noted to be hypotonic at 6 months, when she started to have seizures. At 10 months, she could roll over, was babbling, and could feed herself with a biscuit. She sat at 12 months, but at 20 months was not pulling to stand or crawling. She was a happy child who spoke a couple of words, smiled, and laughed frequently. By 2 years she had made no further progress and speech was still limited to two words.

On examination at 2 years she had a wide face with midfacial hypoplasia and tongue thrusting, and a tendency to clasp her hands together and touch her tongue. She sat with a rounded back. She had jerky movements of the trunk and limbs. Head circumference was 46.2 cm (just above the 3rd centile). CT scans and chromosomes were normal. EEG showed a moderate abnormality during sleep with frequent small discharges over the right fronto-centrotemporal region not accompanied by clinical changes.

On review at 4 years, her jerky movements had almost disappeared and she no longer had a happy disposition. She tended to wring her hands and put her clasped hands in her mouth. She had lost her pincer grip and her ability to finger feed. She was still having seizures, but did not have episodic hyperpnoea, and had acquired microcephaly with a head circumference of 47 cm.

Case report 2 (fig 2)
This girl presented at 2 years 8 months and was the first child of unrelated Caucasian parents. Following a normal term pregnancy, delivery was complicated by meconium stained liquor and she required intubation briefly. She weighed 2670 g, was floppy, and fed poorly. She smiled very late and did not follow with her eyes until 2 years. Her vision and hearing were thought to be normal. She started to babble and had a few words with meaning from 2 years and could drink from a beaker. She was unable to roll over by 2 years 8 months and had just developed slight jerking of one or all limbs which was thought to be myoclonic.

On examination, she was a microcephalic (head circumference 45 cm), fair haired girl with a prominent lower jaw who tended to protrude her tongue. She had repetitive flapping and flicking hand movements but did not bring her hands together or put them in her mouth. She babbled and smiled but did not have episodic hyperpnoea. She had a scoliosis and a rather hairy back. When pulled to sit she was very shaky, but would take weight on her feet fairly steadily. She was generally hypotonic but not weak and had normal reflexes. CT scan and chromosomes were normal. EEG showed a moderate abnormality with low amplitude activity over both hemispheres and isolated discharges seen over the middle third of the head especially during drowsiness, with some poverty of appropriate rhythmic activity for the child's age.

On review at 5 years, there was clear evidence of regression. She had no voluntary hand movements and had mainly one handed stereotypies. She could sit alone for only a few seconds, and had limited head control. She had minimal interaction with the environment and had stopped babbling and said only an occasional word. She had seizures every few months.

I SCHEFFER, E M BRETT, J WILSON
Department of Neurology,
The Hospitals for Sick Children,
Great Ormond Street,
London WC1N 3JH.

M BARAITSER
Department of Clinical Genetics,
The Hospitals for Sick Children,
Great Ormond Street,
London WC1N 3JH.

Recurrence of acheiria in a second cousin: extremely large pedigrees may include ‘second cases’ by chance

Lamont and Salisbury report unilateral absence of the hand (acheiria) in an index case and in a second cousin. In their opinion the possibility that “both children could have been affected by chance . . . is too remote to be considered”. They found no common environmental factor, and proposed a “common mutant dominant gene”, transmitted from one of the shared grandparents, as “the most cogent explanation”. While not denying the logic of their suggestion, nor the evidence from recurrences of acheiria in sibs and in second and third degree relatives, as mentioned in their paper, we wish to point out that if one records pedigrees so as to include second cousins (fifth degree relatives) of the index case one is potentially including data on a very large number of persons indeed, and ‘recurrences’, on a chance basis, are not as unlikely as may initially appear to be the case.

Assuming a simple family structure of two children for every pair of parents (that is, a steady state, non-expanding population), and the recording, in the genetics clinic, of families to include only sibs, parents, grandparents, uncles/aunts, and first cousins of the index case, one would record data on 1 + 2 + 4 + 4 + 8 = 13 other persons per family. Enlarging the pedigree to include second cousins, with the more recently born of their linking relatives, one would record four great uncles/aunts, eight first cousins once removed, and 16 second cousins, that is, a total of 41 relatives of the index case. Were one to include all first to fifth degree relatives in previous or contemporary generations (eight great grandparents, 16 great great grandparents, etc) one would obtain a total of 137 relatives per family, while still excluding generations younger than the index case.

Although we believe no families would possess information on all first to fifth degree relatives (that is, our estimate of 137 relatives is in that way unrealistic), our model of a family with only two children for each two parents underestimates family size. In our clinics we routinely record pedigrees to include grandparents, uncles/aunts, and first cousins, and examining the files of the first 25 families seen in Oxford in 1989 (referrals to a general genetics clinic) we found a total of 475 such relatives of the index cases, that is, an average of 19 per family (not 13, as would be expected on the ‘simple’ model). This suggests that our estimate of 41 relatives per family, if one extends to include second cousins, is also an underestimate. We found 4·68 uncles/aunts instead of the ‘expected’ two, and 7·32 first cousins instead of the ‘expected’ four, that is, each grandparental pair had on average 3·34 (4·68/2 + 1) offspring rather than two, and each of these persons had an average of 1·56 (7·32/4·68) live children at the time the pedigree was constructed. Assuming that fertility was no less in the previous (great grandparental) generation, we calculate an average of 9·36 great uncles/aunts, 31·26 first cousins once removed, and 48·89 second cousins, that is, a total of 108·51 relatives of the index case if families were to be recorded in this way (omitting all generations before the grandparental or after the index case).

Lamont and Salisbury give a birth prevalence for acheiria of 1 in 65 000. With about 600 000 live births in the UK per annum one would expect 92·3 births with acheiria within the last decade, and these would have a total of 10 015 relatives up to and including second cousins (92·3 × 108·51). The probability of acheiria, by chance, among these relatives would be 10 015/65 000 = 0·1541, and from the Poisson distribution the chance of one or more such families actually existing would be 14·28%.

However, Lamont and Salisbury quote an old reference for the birth prevalence of acheiria. From the Edinburgh Register of the Newborn, Rogala et al. found birth prevalence of isolated transverse scapular absence defects to be 0·4 per 10 000, and this is in agreement with estimates one can make combining information from Birch-Jensen and from Wynne-Davies and Lamb. With this prevalence we would expect 240 UK cases in a decade, 26 042 extended family members, and a 64·7% chance of one or more families with recurrence on a chance basis. For all types of transverse forearm/hand defect the birth prevalence is much higher (5·8 per 10 000 from Wynne-Davies and Lamb), and one would expect 3480 UK cases within a decade, with 377 614 extended family; about 6% of these cases would be ‘familial’.

In conditions with a high birth prevalence the likelihood of chance recurrence within an extended family is considerable, and in general one should beware of arguing from such recurrences unless the necessary calculations have been made and a coincidence appears truly unlikely.

Richard Lindenaum, Helen Firth
Department of Medical Genetics, Churchill Hospital, Headington, Oxford OX3 7LT.