Clinical features in four patients with Angelman syndrome resulting from paternal uniparental disomy

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Abstract
Angelman syndrome (AS) is a complex neurological disorder with different genetic aetiologies. It is not known whether the clinical features vary depending on the genetic mechanism. We report four patients with AS owing to uniparental disomy (UPD). There were two males and two females, with a mean age of 8 years (range 7 to 11 years). All patients had a happy disposition, hyperactive behaviour, and the characteristic facial phenotype of AS, but in three there was a normal head circumference, two had epilepsy, ataxic movements were mild in three, the mean age of onset of walking was 2.4 years, and there was some sign language in all four patients. Our cases add further weight to the previously reported impressions of a milder phenotype in cases of AS resulting from UPD than in deleted AS patients. Patients suspected of having AS, but who are considered atypical, warrant DNA testing.

Methods
Patients with the clinical suspicion of AS were referred from Australia and New Zealand for genetic testing under a research grant protocol, approved by the institutional ethics committee. Clinical information was obtained from the data sheet accompanying each referral, correspondence with referring doctors, hospital records, baby health centre records, and parent interviews. All were last reviewed in March 1996.

DNA analysis
Molecular studies (performed during 1991 to 1994) used standard techniques. Polymorphism analysis was performed with probes for loci from within the PWS/AS region (D15S18, D15S9, D15S11, D15S13, D15S128, D15S10, D15S113, D15S97 (GABRB3), D15S98, D15S108, D15S12) and outside the region distally on chromosome 15q (D15S24, ACTC, THBS1, D15S87, D15S86). Informative polymorphisms showing UPD in the four patients are shown in Table 1.

Results and discussion
We have presented the features of four patients with AS resulting from paternal UPD (figs 1, 2, and 3). All patients showed a characteristic facial appearance with large mouth and chin, a happy disposition, outbursts of laughter, hyperactive behaviour, no speech, and severe intellectual disability. Drooling and mouthing were present in all cases, but were not pronounced features. Additional clinical information for each of the four patients with UPD is given in Table 2A. The mean age of diagnosis was 6.25 years and mean age at last review was 8.25 years. All patients were ataxic but in three (cases 28, 29, and 31) the ataxia was mild and most evident when excited. The mean age of onset of walking was 2.4 years, with all walking by 3 years of age. Epilepsy (onset at 1.5 and 4.5 years) was present in two patients. Two patients, at 7 and 8 years of age, had never had a seizure of any type and were not on anticon-
vulcant therapy. The EEG was abnormal in 3/3 patients tested. The characteristic slow spike and wave forms associated with AS were reported in these tracings. One patient (29) was clearly hypopigmented compared to his family (fig 2). He did not have albinism, but hypopigmentation could occur with isodisomy UPD if the patient received two copies of a mutant pigmentation gene from his father. This was not tested here. Both height and head circumference was normal for three patients, while one was short and one was microcephalic. Head circumference and height centiles were concordant for two patients, but discordant in two (patients 28 and 31). In two patients, the weight was over the 50th centile.

We compared our data with 10 other reported cases of AS resulting from UPD (table 2B). Varying details are presented with scant clinical information in some. The mean age of these reported cases was 7.5 (range 3-30) years, similar to our cohort (8.25 years). The head circumference was normal in 10/14 (71.5 %) patients reported. Including our data, 4/14 patients had microcephaly, a frequency of 28.5%. Over all, height was on the 3rd centile or less in 3/13 (23%) patients and normal in 10/13 (77%). Weight was over the 50th centile in 7/11 (64%) of patients. In the reported cases, seizures had occurred in 3/8 patients when, combined with our data, shows that the occurrence of epilepsy was 5/12 patients (42%). All patients tested had an abnormal EEG. Ataxia was mild in 4/13 (31%) ambulant patients. One patient was not ataxic.

The mean paternal age for the combined data on nine cases was slightly raised at 32.5 years. The mean maternal age for the combined data on 11 cases was normal at 28.25 years. This is of interest as mechanisms leading to paternal UPD include paternal meiotic nondisjunction followed by trisomic rescue, iso-chromosome formation, and maternal non-disjunction followed by monosomy rescue. One of our patients had a translocation which, combined with the reported studies (table 2),

Table 1 Pattern of informative DNA markers for the four patients with UPD

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<th>D15S11</th>
<th>D15S13</th>
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Table 2 Patient data (A) and published clinical descriptions of Angelman syndrome owing to paternal UPD (B)

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<th>HR centile</th>
<th>WR centile</th>
<th>E</th>
<th>EEG</th>
<th>A</th>
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ID = under A, patient identity number and under B, reference number; S = sex; AD = age at diagnosis (in years); R = age at last review (in years); BW = birth weight (in grams); HCR = head circumference at last review; HR = height at last review; WR = weight at last review; E = epilepsy with age of onset (in years) where applicable; W = weight of walking alone (in years); At = ataxia; P = pigmentation; SL = sign language with number of words; MA = maternal age and PA = paternal age at birth of the proband; K = karyotype; * = both parents tall; † = preterm; NA = not applicable; ND = not done; fam = familial, namely pigmentation appropriate for the family; H = hypopigmentation compared to the family; abn = abnormal; m = mild; % = patient on anti-convulsant medication; N = normal; t = translocation; id = inv dup(15). Information not filled in indicates that this feature was not mentioned in the published case reports.
patients resulting from DNA deletion can be made (table 3). The dele- 
tional cases come from two surveys, 37 from Japan16 and 27 from 
Australasia.17 It appears that the facial pheno-
type is similar with all patients having a large 
mouth and chin, happy disposition, and 
outbursts of inappropriate laughter. There 
appear to be differences, however, in growth 
parameters and brain maturation (table 3). 

Growth in patients with UPD appears to be 
less retarded; these patients overall have a 
larger head circumference than those with 
deletion, weigh more, and are not as short. A 
higher level of brain function is manifest in 
the earlier age of onset of walking, milder ataxia, 
lower frequency of epilepsy; and greater ability 
to use sign language. Formal psychological 
testing of more cases is required to confirm the 
higher level of brain function suggested here. 
The implications of our findings for the 
diagnosis of AS are to broaden the guidelines 
for testing in patients suspected of AS and to 
test those who might be considered atypical by 
some physicians.

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