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

A Smith, R Marks, E Haan, J Dixon, R J Trent

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.

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Angelman syndrome (AS) is a severe neurodevelopmental disorder with a complex genetic aetiology. Since the first report of three children,¹ the clinical phenotype has become more defined and comprises severe intellectual disability, epilepsy, lack of speech, ataxic movements, outbursts of inappropriate laughter, large mouth and chin, microcephaly, an abnormal EEG, and hypopigmentation in some patients.²⁻³ The phenotype may be variable, and cases have been described as atypical.⁴ The availability of DNA testing has enabled a genetic classification of AS. Four groups are now recognised: (1) maternal deletions of chromosome 15(q11-13) (about 70% of cases), (2) paternal uniparental disomy of chromosome 15 (about 2%), (3) an abnormality in the imprinting process (about 3%), and (4) a mutation affecting a putative AS gene in the remainder.⁵ The chromosome 15(q11-13) region also contains the Prader-Willi syndrome (PWS) locus. This region is subject to genomic imprinting, whereby the expression of the gene(s) is dependent on the parent of origin.⁶ In AS the locus on the paternally derived chromosome 15 is imprinted and cases with UPD have inherited both copies of the chromosome

15 from the father and none from the mother. The parental origin is the reverse in PWS.

Cases of AS resulting from UPD are rare and only a few reports have been published with detailed clinical descriptions.⁷⁻¹⁴ In this report we describe four new patients with AS resulting from paternal UPD, to broaden the knowledge of this genetic type.

Methods

PATIENTS

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.¹⁵ 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.¹⁵⁻¹⁶ 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-

Department of
Cytogenetics, New
Children's Hospital,
Hawkesbury Road,
Westmead, NSW 2145,
Australia
A Smith

Developmental
Paediatrics, Starship
Children's Health,
Auckland, New
Zealand
R Marks

Department of
Medical Genetics,
Women and Children's
Hospital, Adelaide,
Australia
E Haan

Department of
Genetics and
Paediatrics, Wellington
Hospital, New Zealand
J Dixon

Department of
Molecular Genetics,
Royal Prince Alfred
Hospital, Sydney,
Australia
R J Trent

Correspondence to:
Dr Smith.

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

Family	DNA probe					
	D15S11	D15S13	D15S113	D15S97	D15S98	D15S108
Patient 28	b	d			c	
Mother	c	bc			ab	
Father	ab	ad			cd	
Patient 29		b	d		c	
Mother		c	bc		ab	
Father		ab	ad		cd	
Patient 30					c	c
Mother					ab	ab
Father					ac	ac
Patient 31	ac		ab	a		a
Mother	b		c	b		b
Father unknown						

vulsant therapy. The EEG was abnormal in 3/3 patients tested. The characteristic slow spike and wave forms associated with AS¹⁷ 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 which, when combined with our data,

Figure 1 Patient 28 aged 7 years.

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.¹²

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 non-disjunction followed by trisomic rescue, isochromosome formation, and maternal non-disjunction followed by monosomy rescue.¹⁸ One of our patients had a translocation which, combined with the reported studies (table 2),

Table 2 Patient data (A) and published clinical descriptions of Angelman syndrome owing to paternal UPD (B)

ID	S	AD/R	BW	HCR centile	HtR centile	WtR centile	E	EEG	W	At	P	SL	MA	PA	K
<i>A</i>															
28	F	4/7	3700	25	75*	50	No	abn	2	m	fam	10	22	25	N
29	M	7/8	4000	25	25	10	No	ND	2	m	H	15	28	32	N
30	F	9/11	2180†	2	3	> 97	1.5	abn	2.5	Yes	fam	8	25	31	N
31	M	5/7	3420	25	50	90	4.5	abn	3	m	fam	35	19	NK	t
<i>B</i>															
7	F	4/4	3550	10			Yes	abn	No	NA					N
	M	2/6	N	3	25	10		abn	Yes						N
8	F	4.5/4.5	3150	70	50	90	No	abn	2	Yes					t
9	M	2.5/3	3954	< 5	75	75	No	abn	3	Yes			33	26	N
10	M	4/4	2990	N	N	N	No‡	abn	2	Yes	fam		30	40	id
11	M	3/3	4100	75-90	10-25	> 95	No	abn	3	Yes			31		t
12	F	7.5/7.5	2970	10-25	90-97	97	4.5	abn	2.5	m		Yes	43	45	N
	F	3/10	3210	10-25	10-25	75-90	No‡	abn	2.5	No		Words	31	43	N
13	M	25/30	3380	50	3	50	2	abn	2.5	Yes	fam	No	24	26	t
14	M	2/3	3460	< 3	< 1			abn	2.5	Yes	fam		25	25	N

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; HtR = height at last review; WtR = weight at last review; E = epilepsy with age of onset (in years) where applicable; W = age 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; NK = not known; ND = not done; fam = familial, namely pigmentation appropriate for the family; H = hypopigmented 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.

Figure 2 Patient 29 aged 8 years. Note the fair hair and white eyebrows.

gives overall 5/14 (36%) of AS patients with UPD having a structural rearrangement involving chromosome 15(q11-13). This high frequency suggests that structural rearrangements of chromosome 15 predispose to malsegregation at meiosis. More detailed DNA studies on structural rearrangements of chromosome 15 in general are required to confirm this suggestion.

The observation that the AS phenotype can be influenced by the underlying genetic mechanism is of interest in the understanding of how imprinted genes are expressed.⁶ In PWS, valid comparative clinical data are scant but current evidence suggests that there are no differences in the phenotype of those with a deletion compared to those with UPD.¹⁹ Given that the size of the deletion in over 90% of PWS and AS patients is the same,⁶ it would appear that there is some fundamental biological difference in the expression of the imprinted gene(s) for PWS and AS.

Valid comparisons of the data presented here in 14 cases of AS resulting from UPD with AS

Figure 3 Patient 30 aged 11 years.

patients resulting from DNA deletion can be made (table 3). The deletional cases come from two surveys, 37 from Japan²⁰ and 27 from Australasia.¹⁵ It appears that the facial phenotype 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.

Table 3 Comparison of those features showing statistically significant differences between patients with AS owing to DNA deletion and those with UPD (in %)

Feature	Deletion*	UPD†	p value‡
Microcephaly	62.5	28.5	0.09
Height < 3rd centile	81	23	0.0064
Weight > 50th centile	15	64	0.073
Seizures	~100	42	0.0056
Walking by 3 years	37	100	0.0063
Hypopigmented	73	25	0.042
No/mild ataxia	0	38.5	0.0048

* References 15, 20.

† Table 1.

‡ Application of the Fisher's exact test indicated wide confidence limits for each parameter with the limited information available.

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