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Problem Behaviors Associated With 15q- Angelman Syndrome

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Caregivers of persons with Angelman syndrome completed the Aberrant Behavior Checklist and Reiss Screen for Maladaptive Behavior. Seventy-three replies were received, and comparisons were made with other published data. Responses indicated that 15q- Angelman syndrome is associated with such problems as lack of speech, overactivity, restlessness, and eating and sleep problems. Episodes of inappropriate laughter were only reported for 57%, despite being considered a cardinal feature of the syndrome; eating problems (64%) and a fascination with water (68%) were reported more frequently. Overactivity was more of a problem for children; Aberrant Behavior Checklist Factor IV (Hyperactivity) was negatively correlated with age. Scores were mostly lower than for previously studied etiological groups. Therapeutic effort should be put into programs to address these problems.

Angelman syndrome, first described in 1965 (Angelman, 1965), is characterized by low birthweight, neonatal feeding problems, poor weight gain in infancy, and a propensity to gastroesophageal reflux in childhood. Facial dysmorphology includes a wide mouth, thin upper lip, pointed chin, prominent tongue, and widely spaced teeth. Motor development is delayed, and there is usually a widely based, stiff-legged, ataxic gait in adult life, often associated with tremulousness and jerky movements. These clinical features led to the term *happy puppet* being used in the 1960s and 1970s to describe the syndrome. The term is considered offensive by many people with the disorder and their caregivers and probably does not accurately describe the sudden bursts of inappropriate laughter that occur in the syndrome. The associated mental retardation is usually severe.

Results of electroencephalograms (EEGs) given to individuals with Angelman syndrome are relatively characteristic, with large amplitude slow wave activity, more prominent anteriorly, which persists during sleep, and spikes or sharp waves mixed with large amplitude components that are more prominent posteriorly and are facilitated by eye closure (Udwin & Dennis, 1995). More than 80% of affected people have seizures, and the epilepsy may be difficult to treat. Clayton-Smith (1993) identified a pattern of episodes lasting several weeks in which seizures occur frequently and are often refractory to treatment, interspersed with seizure-

free intervals of several weeks. Seizures seem to be most problematic around the age of 4 years, often with subsequent amelioration. Little speech develops; individuals typically acquire no more than three words (Udwin & Dennis, 1985).

About 70% of people with Angelman syndrome have small deletions of maternal origin affecting chromosome 15 at 15q11q13. The disorder is also associated with paternal uniparental disomy (the inheritance of two chromosome 15s from the father). The syndrome is believed to be due to the loss of, or absence of expression of, the UBE3A/E6-AP gene (Kishino, Lalande, & Wagstaff, 1997).

Some behavioral characteristics have been reported in association with Angelman syndrome. Sudden outbursts of laughter were described in the initial report (Angelman, 1965). These are often inappropriate to the circumstances and do not necessarily indicate a positive mood state (Clayton-Smith, 1993). Pica, rumination, and repeated placing of objects into the mouth have also been reported (Penner, Johnston, Faircloth, Irish, & Williams 1993). Information about social and communicatory aspects of the disorder is conflicting: Penner et al. found that affected individuals have difficulties in motor functioning, which may reflect an oral motor dyspraxia. They also found limitations in social interaction and communication, whereas Clayton-Smith (1993) and Zori et al. (1992) found that comprehension among individuals with this syndrome was significantly better than their expressive speech and noted that many affected people want to communicate using nonverbal methods, such as signs, gestures, and picture boards. Overactivity and distractibility have been noted, with suggestions that as affected individuals become older, they may improve with regard to these types of behavior (Udwin & Dennis, 1995). Clayton-Smith reported sleep problems, which have also been noted to be less problematic as individuals age. As with many reports on syndromes of genetic origin, however, most examinations of Angelman syndrome have small sample sizes or lack genetic confirmation of the diagnosis, and most investigators have used descriptive methods rather than standardized instruments. Udwin and Dennis, reviewing the literature on behavioral aspects of Angelman syndrome, concluded that "information about the cognitive and behavioural characteristics associated with Angelman syndrome is still largely anecdotal" (p. 95).

In the present study we sought to further such work by investigating a relatively large sample of people with the disorder, limiting the results reported to those people with documented deletions affecting 15q11q13 and utilizing two standardized assessments suitable for the rating of problem behaviors associated with mental retardation. Our intention in studying problem behaviors was to pave the way for effective interventions. Our intention was not merely to emphasize the problematic behaviors of individuals with the syndrome. Indeed, many caregivers commented on positive aspects of the behavior and personality of people with Angelman syndrome.

Method

With the help of representatives of two parent and caregiver support organizations in the United Kingdom, the Angelman Syndrome Support Group and the Angelman Syndrome Support Education and Research Trust, we mailed a questionnaire to the caregivers of people with the syndrome. The questionnaire consisted of three parts: a section in which respondents were asked for basic information (e.g., height, weight, place and type of residence, and a question about genetic testing); the Aberrant Behavior Checklist, Community Version (Aman, Burrow, & Wolford, 1995; Aman, Singh, Stewart, & Field, 1985a, 1985b); and the Reiss Screen for Maladaptive Behavior (Reiss, 1988), which was to be completed only if the person with Angelman syndrome was age 12 years or

older. To answer the question about genetic testing, the caregiver stated whether a genetic abnormality had been found and, if so, what type of abnormality it was, by whom it had been found, and in which hospital or unit the person finding the abnormality worked. Reasons for using the Aberrant Behavior Checklist, and a detailed discussion of the methodology, are given in Clarke and Boer (1998). The instrument is a 58-item checklist of possible problem behaviors that caregivers are asked to rate on a scale of 0 (not at all a problem) to 3 (the problem is severe in degree). We sent 216 questionnaires to the Angelman Syndrome Support Group and 250 to Angelman Syndrome Support Education and Research Trust, which their representatives forwarded to caregivers associated with their group.

Results

Replies were received from the caregivers of 181 people who were members of one of the groups. This equates to a response rate of at least 38.8% because many caregivers received questionnaires from both groups, but a definite figure for the degree of overlap in mailing could not be established. The authors and representatives of the two caregiver groups agreed that only one mailing would be made to caregivers identified by each organization. Almost all caregivers were parents, usually mothers. Of the 181 replies received, 87 related to people for whom a definite genetic abnormality had not been found or for whom details of the person or unit establishing the genetic diagnosis were not given. A further 17 replies were excluded because they related to children below 5 years of age (the Aberrant Behavior Checklist is intended for adults and children of 5 years of age and over), and 5 replies because the genetic abnormality found was uniparental disomy rather than a deletion affecting 15q11q13. The final sample contain information on 73 people with Angelman syndrome who had a documented deletion within 15q11q13 and who were at least 5 years old.

Basic demographic information and Aberrant Behavior Checklist factor (subscale) scores are given in Table 1. Table 2 details z scores (number of standard deviations [*SD*s] separating the means) for the three deletion syndromes compared to the mean Aberrant Behavior Checklist subscale scores reported by Aman and Singh (1986) in the Aberrant Behavior Checklist manual; these persons were ages 5 to 51+, resided in institutions, and had predominantly severe or profound mental retardation. To ensure comparable ages in the two groups (Angelman syndrome and Aman and Singh's population), we combined the age ranges between 5 and 50 reported by Aman and Singh and excluded the 51+ age band.

Table 1
Characteristics of the Individuals With 15q- Angelman Syndrome

Characteristic	Mean or *n*	*SD* or %
Mean age[a]	11.0	5.7
Mean weight (kg)	33.45	15.22
Mean height (m)	1.34	0.19
Mean body mass index (kgm²)	19.14	4.77
Severity of retardation (*n*)[a]		
None	0	—
Mild	0	—
Moderate	2	—
Severe	47	—
Profound	11	—
Mean ABC factor[b]		
I	8.74	7.64
II	4.93	5.27
III	4.34	4.45
IV	20.08	11.38
V	0.43	1.11
Point prevalence of (*n*, % of 72)		
No speech	59	82
Can only use a few words	12	17
Seizures	65	90
Jerky movements	66	92
Episodes of inappropriate laughter	41	57
Place of residence (*n*, %)		
Family home	66	90.4
Community residential facility	4	6.8
Hospital	1	1.4
Residential school	1	1.4

Note. Sample consisted of 73 individuals (38 males, 35 females), ranging in age from 5 to 33 years.
[a] $N = 60$. Severity levels reported by caregivers. [b] Aberrant Behavior Checklist factors: I = Irritability, Agitation, II = Lethargy, Withdrawal, III = Stereotypic Behavior, IV = Hyperactivity, Noncompliance, V = Inappropriate Speech.

Table 2
Comparison of Z scores for Mean Aberrant Behavior Checklist Factors by Standardization Sample

Standardization sample	ABC factor[a]				
	I	II	III	IV	V
Aman & Singh[b]	−0.034	−0.410	−0.177	0.782	−0.406
Marshburn & Aman[c]	0.191	−0.034	0.536	0.651	−0.440

[a]Aberrant Behavior Checklist (ABC) factors: I = Irritability, Agitation, II = Lethargy, Withdrawal, III = Stereotypic Behavior, IV = Hyperactivity, Noncompliance, V = Inappropriate Speech. [b]Aman and Singh's (1986) group, which contained 688 persons with mental retardation ages 5 to 50 who lived in institutions. *N* = 72 individuals with 15q- Angelman syndrome. [c]Marshburn and Aman's (1992) 539 students with mental retardation ages 6 to 21 who lived in community settings. *N* = 61 individuals with 15q- Angelman syndrome. *Z* scores obtained by recalculating mean ABC scores for 15q- Angelman syndrome group to exclude people who were less than 6 years or over 21 years and using Table V from Marshburn and Aman as standardization sample.

Table 2 also shows a comparison between our subset of people with 15q- Angelman syndrome 6 to 21 years of age and Marshburn and Aman's (1992) 539 people with mental retardation between 6 and 21 years of age who resided in community settings. The comparison with Aman and Singh's (1986) data is more appropriate for the severity of mental retardation of the Angelman syndrome sample, whereas the comparison with Marshburn and Aman's data is probably most valid when residential placement (i.e., in family homes or other community settings rather than in institutions) is considered. We also made similar comparisons for 15q- Prader-Willi syndrome, 17p- Smith-Magenis syndrome, and 5p- Cri-du-Chat syndrome (Clarke & Boer, 1998), allowing comparisons of scores obtained for 15q- Angelman syndrome with those obtained for the other chromosome deletion disorders (see Table 3). The *z* scores indicate the distance (in *SD*s of the standardization group) between the mean of the study sample and standardization group. About 65% of the standardization group would be expected to have scores between ±1. The factor scores for 15q- Angelman syndrome suggest a characteristic pattern of problem behaviors, but the magnitude of the scores is much lower than that for disorders such as Smith-Magenis syndrome (Factor V score = 1.85) and Prader-Willi syndrome (Factor V score = 1.08).

Table 4 shows the highest scoring items on the Aberrant Behavior Checklist and Reiss Screen. This is clinically informative, confirming that the behaviors identified as most problematic by caregivers concern overactivity, sleep problems, impulsivity, and unwillingness or inability to use verbal prompts regarding behavior.

In view of the clinical suggestions that overactivity becomes less problematic with increasing age, we correlated Aberrant Behavior Checklist Factor IV (Hyperactivity and Noncompliance) scores with age. The result confirmed that hyperactivity was negatively correlated with age, $r(71) = -.36$. Other correlations of Aberrant Behavior Checklist factor scores with age were nonsignificant. The overall difference in scores between the Angelman syndrome and contrast groups for Factor IV does not appear to be great but masks a great difference in Aberrant Behavior Checklist Factor IV scores between Angelman

Table 3
Summary of Data From Studies of Other Syndromes and Comparison With 15q- Angelman Syndrome

		Factor[a]									
		I		II		III		IV		V	
Syndrome	*n*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
15q- Angelman syndrome	73	8.74	7.64	4.93	5.27	4.34	4.45	20.08	11.38	0.43	1.11
5p- syndrome	43	12.47	8.86	4.60	6.65	5.05	5.16	20.53	11.08	2.12	3.33
15q- Prader-Willi syndrome	34	14.53	10.24	6.15	6.13	1.10	1.29	9.12	6.55	4.15	2.84
17p- Smith-Magenis syndrome	26	21.88	12.79	7.08	5.55	6.88	5.18	23.46	12.15	5.19	3.87

[a]Aberrant Behavior Checklist factors—I = Irritability, Agitation, II = Lethargy, Withdrawal, III = Stereotypic Behavior, IV = Hyperactivity, Noncompliance, V = Inappropriate Speech.

Table 4
Highest Scoring on Instrument Items

Instrument/Item	Mean score
Aberrant Behavior Checklist[a]	
Is easily distractible	1.97
Tends to be excessively active	1.54
Excessively active	1.50
Restless, unable to sit still	1.46
Disturbs others	1.46
Does not pay attention to instructions	1.40
Demands must be met immediately	1.39
Will not sit still for any length of time	1.33
Disobedient, difficult to control	1.31
Impulsive (acts without thinking)	1.26
Reiss Screen[b]	
Sleep problem	1.20
Attention seeking	0.84
Dependent	0.84
Overactive	0.76
Destructive	0.72
Impulsive	0.60
Unusual motor movements	0.60

[a]Range = 0 to 3. [b]Range = 0 to 2.

syndrome subjects above and below 16 years of age. To compare these subgroups, we used the Wilcoxon test and found a significant difference, $z = 2.295$, $p = .02$, further demonstrating an effect of age on this subscale for persons with 15q- Angelman syndrome. However, some researchers (e.g., Rojahn & Helsel, 1991) have found similar correlations in other groups of people with mental retardation, so the effect may not be specific to 15q- Angelman syndrome.

We used the Reiss Screen primarily to identify sleep problems and symptoms suggestive of psychosis, which are not included within the Aberrant Behavior Checklist. Sleep problems were reported relatively frequently (42%), whereas symptoms of severe mental illness (e.g., delusions, hallucinations, paranoia, suicidal tendencies) were not reported by any respondents. Self-injury was reported as a problem for 10 people, and a major problem for an additional person, out of 25 people over the age of 12 years for whom the Reiss Screen was completed. Euphoria was reported as a problem for 9 people, and a major problem for an additional person. The mean item ratings for Aberrant Behavior Checklist items relevant to psychiatric disorder were .63 for "odd, bizarre in behavior," .06 for "depressed mood," and .63 for "mood changes rapidly." Reiss Screen scores also confirmed the high prevalence of overactivity (problem for 9 people, major problem for 5 additional people; overall prevalence 56% among people over 12 years of age). The Reiss Screen is not applicable to persons below 12 years of age, for whom the Aberrant Behavior Checklist data suggest a higher prevalence than in older people.

Table 5 documents other problem behaviors or unusual behaviors reported by caregivers in response to an open-ended question. Fascination with water was given as an example, because it had previously been suggested as common in Angelman syndrome. The other behaviors were reported without prompting.

Table 5
Reports of Other Behaviors

Behavior	*n*[a]	%
Eating problems (overeating, narrow range of food preferences, etc)	46	64
Mouthing or trying to eat non-food items	35	49
Sleep problems	30	42
Fascination with plastics, rubber, etc	16	22
Fascination with water, excessive water play[b]	49	68

[a]$N = 72$. [b]A prompt was provided for this item. Other behaviors were reported without prompting.

Discussion

The present study is the largest published behavioral survey, in which standardized assessments were used, of people with deletion Angelman syndrome. The results lend further support to the view that deletion Angelman syndrome is associated with a pattern of behaviors (a behavioral phenotype) characterized by overactivity, restlessness, eating and sleep problems, and a fascination with water and some other materials in addition to the lack of speech development previously reported. Results of the present study support the hypothesis that hyperactivity becomes less problematic with age, although longitudinal studies would be necessary to confirm that this is an effect of aging rather than a cohort

effect. The very low Aberrant Behavior Checklist Factor V (Inappropriate Speech) score reported in this study probably reflects the lack of speech development associated with Angelman syndrome. None of the individuals with15q- Angleman syndrome had psychotic symptoms in contrast to relatively frequent reports in association with 15q- Prader-Willi syndrome (Clarke, 1998; Clarke et al., 1998; Verhoeven, Tuinier, & Curfs, 1998). This finding may be of relevance to understanding genetic influences on psychotic symptoms because Angelman syndrome and Prader Willi syndrome result from failure of expression of oppositely imprinted genes within 15q11q13, probably one gene in the case of Angelman syndrome (Kishno, Lalande, & Wagstaff, 1997) and several genes in Prader Willi syndrome. The finding must be treated with caution, however, in view of the great difficulty in detecting complex psychopathology, such as abnormal beliefs or auditory hallucinations in persons with no, or very little, speech.

The present study has a number of methodological weaknesses. The sample may not be entirely representative of 15q- Angelman syndrome because caregivers were contacted via support organizations and the response rate was not high, introducing a probable bias to the inclusion of people from families of higher than average social and educational background (who may be more likely to join such an association and to reply to written requests for information). However, the reported response rate is a minimum figure, for reasons outlined earlier. Further studies involving direct observation would be helpful to confirm the findings, which are based on caregiver reports. Many professionals have suggested that parents may report behaviors believed to be associated with a genetic disorder rather than behaviors they have observed. However, in the one study (on Williams syndrome) in which this hypothesis could be tested, Einfeld, Tonge, and Florio (1997) found no evidence of such an effect. The methodology we used, which is discussed more extensively in Clarke and Boer (1998), has the advantage of being user-friendly and relatively inexpensive and can, therefore, be employed for follow-up studies. A comparison with subjects matched for age, gender, and severity of mental retardation would be a more robust methodology, as in Clarke, Boer, Chung, Sturmey, and Webb (1996), but proved impractical for this study because of the difficulty in obtaining adequate numbers of younger people with severe mental retardation to act as contrast subjects. The use of published norms for comparison is a less robust method but does allow some conclusions to be drawn about behaviors that appear particularly problematic.

We regard our findings as a preliminary phase in the investigation of such problem behaviors, which should be supplemented by research on other samples and by using other methodologies such as direct observation. We consider it to be useful (in the absence of other published work) as an indicator of which behaviors are perceived as being most problematic in specific genetic disorders. This may help guide clinicians and researchers who may have strategies to alleviate such problems and may have other benefits, such as prompting a consideration of the diagnosis of particular genetic disorders in children with behavioral syndromes that include, for example, hyperactivity. Ultimately, we hope that our research will pave the way for a better quality of life for people with genetic disorders as a result of increased recognition and treatment of problem behaviors.

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