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Cognitive and Adaptive Behavior Profiles of Children With Angelman Syndrome

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Angelman syndrome (AS) is a neurodevelopmental disorder caused by maternal deficiency of the *UBE3A* gene that encodes E6-AP ubiquitin-protein ligase. Expression of the *UBE3A* gene from the maternal chromosome is essential to prevent AS. AS is characterized by severe mental retardation, ataxia, and a defined behavioral pattern characterized mainly by happy/sociable disposition. This study used the Bayley Scales of Infant Development and the Vineland Adaptive Behavior Scales to examine the cognitive abilities and adaptive behavior of children (n = 20) with the four known molecular classes of AS, including patterns of strengths and weaknesses across adaptive behavior domains, and the relationship between adaptive behavior and overall cognitive abilities. Cognitive skills fell within the severe to profound range of mental deficiency. Differences in cognitive skills according to genetic subtype only partially supported previous research and suggest that there is overlap in abilities across genetic subtypes of AS. Adaptive behavior skills were also significantly delayed, with participants demonstrating a significant strength in socialization, and a weakness in motor skills. Strong, positive correlations emerge between cognitive ability scores and adaptive behaviors scores. These results provide further delineation of a cognitive/behavioral phenotype in AS.

KEY WORDS: Angelman syndrome; chromosome 15; intelligence; adaptive behavior

INTRODUCTION

Angelman syndrome (AS) is a neurodevelopmental disorder characterized by severe mental retardation, ataxia, and a happy/sociable disposition. It is now known that expression of the *UBE3A* gene from the maternal chromosome is essential to prevent AS [Kishino et al., 1997; Matsuura et al., 1997].

Some descriptive studies have demonstrated slight differences in the functioning of children with AS according to genetic subtype [Lossie et al., 2001]. Specifically, they find that children with the typical deletion have severe to profound mental retardation, are nonverbal, and walk later than children with other genetic subtypes of AS [Lossie et al., 2001]. In addition, some studies have suggested that children with UPD have higher cognitive skills, have a delayed onset of seizures, and have fewer motor difficulties [Bottani et al., 1994; Gillessen-Kaesbach et al., 1995; Fridman et al., 2000]. Other case reports, however, have not found that children with UPD have a "milder" phenotype, and the researchers hypothesize that differences in functioning may be attributable to differences in *UBE3A* expression from the paternal allele [Smith et al., 1994; Prasad and Wagstaff, 1997].

Despite descriptive data documenting the cognitive and behavioral profiles of children with AS, very few studies have utilized standardized instruments to examine these profiles. One study utilized the Griffiths' Mental Development Scale (birth–2-year-old version) [Association for Research in Infant and Child Development, 1996], and found that the cognitive abilities of AS children fell between the ages of birth–2 years, regardless of a child's chronological age [Andersen et al., 2001]. Adaptive behavior profiles were not explored as part of this study.

Virtually no studies have utilized standardized instruments to explore adaptive behavior profiles of children with AS. One formal study evaluating the adaptive behavior profiles of children and adults with AS (age range = 3–52) found that mean adaptive behavior composite scores fell at a 16-month level [Duker et al., 2002]. Relative adaptive strengths and weaknesses were not reported. Reports from case studies and questionnaires note that children with AS can learn to make choices/express preferences, can help with dressing and bathing, and can feed themselves using basic utensils [Clayton-Smith and Laan, 2003].

This study attempts to validate phenotypic descriptions of behavior in AS by using standardized tools to examine the cognitive skills and adaptive behavior of children with AS, patterns of strengths and weaknesses across adaptive behavior domains, and the relationship between adaptive behavior and overall cognitive abilities. It was hypothesized, based on case studies of the cognitive and behavioral profiles of children with AS, that the domain of socialization would be a relative strength, while the domains of motor skills (for children under 6) and communication would be relative weaknesses.

METHODS

Participants

Twenty clinical subjects were brought to the General Clinical Research Center at Texas Children's Hospital to

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participate in a research treatment trial protocol. The focus of this study was to examine the therapeutic effects of two medications: betaine and folic acid in children with AS. The protocol rationale was to attempt to promote gene expression from the silent *UBE3A* paternal allele in order to ameliorate the clinical symptoms of AS. Further details of this study will be published in the near future. Twenty children received evaluations from a clinical geneticist, a neurologist, and a psychologist at 0, 6, and 12 months. One child was excluded from this analysis because different assessment instruments were utilized to evaluate his cognitive skills at baseline.

All of the participant's diagnoses of AS were confirmed by molecular testing prior to enrollment. Of the 19 patients, 15 had the common large deletions, 2 had paternal UPD, one had a UBE3A mutation, and one had an imprinting defect without a deletion of the AS-IC.

Participants ranged in age between 5 months and 10 years at enrollment, with a mean of 3 years, 8 months, and SD of 2 years, 5 months. There were 11 males and 9 females. Two of the children were of Hispanic descent, 1 was African-American, and the remaining 17 children were Caucasian. Since the focus of this paper is on cognitive skills and adaptive behavior, information only from the psychological assessment will be presented. This analysis reflects the initial evaluation performed at 0 months at the beginning of the protocol and prior to the trial medication intake.

Instrumentation

Participants were evaluated using standardized measures to assess cognitive/developmental skills as well as adaptive behavior. The Bayley Scales of Infant Development, Second Edition, Mental Scale (BSID-II) [Bayley, 1993] was used to assess cognitive skills. The BSID-II was chosen as a measure of cognitive ability because children were unable to complete a more age-appropriate measure. Motor skills were also assessed using the BSID-II Motor Scale, but are not reported in this paper. In addition, parents were interviewed using the standardized administration of the Vineland Adaptive Behavior Scales—Interview Edition (VABS) [Sparrow et al., 1984]. These instruments have excellent normative data, have demonstrated good reliability and validity, and yield useful diagnostic information that translates directly to goals for therapeutic intervention for a child.

The BSID-II is a standardized, individually administered evaluation that assesses current developmental functioning of infants and children. The age range for the BSID-II is from birth to 42 months. The BSID-II can be used with older children of lower ability, who fall outside the age range [Bayley, 1993]. If using the scale beyond the normative range, however, performance can only be described in terms of developmental age.

The Vineland Adaptive Behavior Scales, Interview Edition, is a semi-structured interview conducted with the child's primary caregiver. It assesses a child's ability to perform activities of daily living required for personal and social competence. For children under 6 years of age, it yields standard scores in four domains including: communication, daily living skills, socialization, and motor skills. For children over the age of 6, the motor skills domain is not assessed.

RESULTS

Cognitive skills ranged between the developmental ages of 3–17 months. Virtually all children had scores that fell within the severe to profound range of mental deficiency. Results of one-way ANOVAs indicate there were no gender differences between participants when examining raw scores from the BSID-II Mental Development Index ($F = 0.00$, ns). Raw scores were used for this analysis, because many children fell beyond the normative age range of the BSID-II and standard scores could not be computed. Differences between ethnic groups were not formally compared, due to small numbers of children within certain categories.

Although formal statistical analyses could not be completed to compare profiles of children according to different genetic subtypes, because of low numbers of participants with UPD, imprinting defect, and *UBE 3A* mutation, some qualitative differences are noted (see Table I). Table I reflects the developmental age scores and raw scores of children on the BSID-II, as broken down according to each child's chronological age and genetic subtype. Broadly, deletion positive children were among the younger participants in this study. Although it appears that they achieved lower scores as compared to children with other genetic subtypes of AS, the fact that they were not compared to children of their same chronological age prevents making this conclusion. It is notable that one child who is deletion positive achieved one of the highest scores of all participants (equivalent to 16 months), although she was also the oldest child in the study. When examining mean raw scores for the two children with UPD, one of the children (an 8-year-old female) attained the highest score as compared to all other children in the study, regardless of genetic subtype, (equivalent to that of a child around the age of 17 months), while the other child, a 4-year, 8-month-old male, achieved one of the lowest scores as compared to all other children (5 months developmentally). The child who scored lower has a clinically confirmed diagnosis of autism, in addition to AS. During the evaluation, he engaged in several repetitive/stereotypic behaviors, and did not socially reference his mother or the examiner. The one child with *UBE3A* mutation who was evaluated also attained one of the highest scores as compared to other children in the study, as did the child with an imprinting defect.

Table II reflects the scores of children from the Vineland Adaptive Behavior Scales, Interview Edition. Broadly, children were found to be functioning in moderate deficits range of the low adaptive level. Results of one-way ANOVASs revealed

TABLE I. Developmental Age Scores and Raw Score Breakdown According to Chronological Age and Genetic Subtype

Chronological age (months)	Genetic subtype	Developmental age scores	Raw score
5	Deletion	3 months	34
15	Deletion	6 months	61
16	Deletion	5 months	53
23	Deletion	7 months	68
25	Deletion	6 months	65
26	Deletion	7 months	70
26	Deletion	6 months	65
26	Deletion	7 months	68
35	Deletion	6 months	63
40	Deletion	7 months	67
47	Mutation	15 months	101
49	Deletion	9 months	76
51	Deletion	7 months	67
51	Deletion	9 months	76
56	UPD	5 months	54
67	Imp. Defect	14 months	94
69	Deletion	7 months	67
95	UPD	17 months	108
123	Deletion	16 months	103
Total		8.36	71.58

Note, raw scores are depicted because not all children could achieve standardized scores on the BSID-II.

TABLE II. Standard Scores From the Vineland Adaptive Behavior Scales, Interview Edition

Subtest	N	Mean	SD	Min.	Max.
Communication	19	54.47	16.97	23	101
Daily living skills	19	51.33	21.05	<20	98
Socialization	19	60.89	14.22	39	95
Motor skills (for children under age 6)	17	48.76	18.53	<20	84
Adaptive behavior composite	19	49.05	16.75	25	92

there were no significant differences between the adaptive behavior skills of males and females ($F = 0.788$ ns). Repeated measures ANOVAs were conducted to determine whether there were significant differences in Vineland standard scores across the domains of Communication, Daily Living Skills, and Socialization. A main effect of domain was observed $F(2, 17) = 9.99$, $P < 0.01$. A Bonferroni post hoc test was subsequently conducted, and, as predicted, socialization skills were a relative strength as compared to communication and daily living skills. A second analysis was conducted using only children under 6 years of age to consider the Motor Skills domain of adaptive behavior. A main effect for domain was found $F(3, 13) = 17.09$, $P < 0.001$. Results of a Bonferroni post hoc test revealed that, as predicted, motor skills were a significant weakness relative to all other domains, and that socialization was a significant strength relative to all other domains.

In analyzing the relationship between cognitive abilities and adaptive behavior, BSID-II developmental age scores were correlated with VABS age-equivalent scores. Results revealed strong positive correlations for all of the VABS domains: communication $r = 0.74$, $P < 0.001$, daily living $r = 0.80$, $P < 0.001$, socialization $r = 0.85$, $P < 0.001$ and motor skills $r = 0.90$, $P < 0.001$.

DISCUSSION

The current study represents the first standardized evaluation of a population of children with AS to study cognitive abilities and adaptive behavior. This permits comparison of children with AS to those children from other clinical populations, and allows for the examination of unique patterns of strengths and weaknesses in AS.

The results of this study supported previous research demonstrating that AS children function within severe to profound range of mental retardation [Andersen et al., 2001; Lossie et al., 2001]. No child functioned at a developmental level greater than 17 months, therefore reflecting a restriction of range in cognitive functioning in children with AS compared to children with other developmental disorders. This demonstrates the importance of using developmentally appropriate measures (e.g., Bayley Scales of Infant Development) when evaluating children with AS, as opposed to instruments that are appropriate for the child's chronological age.

Differences in cognitive skills according to genetic subtype only partially supported previous research and suggest that there is overlap in abilities across genetic subtypes of AS. First, one of the deletion positive children achieved one of the highest scores of all participants. This may be attributable, however, to her also being the oldest child in the study. Results for children with paternal UPD demonstrated mixed support of previous studies. While one child with UPD achieved the highest score in the study, supporting research suggesting a milder phenotype for children with UPD [Bottani et al., 1994], the other child with UPD achieved one of the lowest scores. The latter finding supports other studies suggesting that children with UPD function at a level equivalent to that of children with the typical maternal deletion [Prasad and Wagstaff, 1997]. One explanation for the disparity in functioning between these children is that the lower-functioning child with UPD has comorbid autism. Autism has been linked with AS [Steffenburg et al., 1996], but only so far for children who have the typical maternal deletion, not for those with UPD [Thompson and Bolton, 2003].

The adaptive behavior skills of children in this study were strongly correlated with their cognitive abilities, therefore, demonstrating the concordance of parental reports of adaptive behavior with the results of standardized cognitive assessment. These findings are consistent with what is observed in other populations of children with genetic syndromes [e.g., Dykens et al., 1994; Carter et al., 1998; Mervis et al., 2002]. The pattern of adaptive behavior strengths and weaknesses in this study matched what was hypothesized, reflecting the domain of motor skills as a relative weakness for children with AS. This supports previous research documenting significant fine and gross motor delays in children with AS [Williams et al., 1995; Lossie et al., 2001; Clayton-Smith and Laan, 2003]. In contrast, socialization skills as measured on the Vineland are a relative strength for children with AS. Because the VABS socialization scale assesses purposeful interactive skills, findings from the present study support research that indicates that smiling and laughing behaviors in children with AS increase in social situations, and decrease during non-social situations [Oliver et al., 2002]. This is in contrast to previous studies that reported that the laughter observed in AS is not always socially directed and may occur without a stimulus [Robb et al., 1989; Summers et al., 1995].

This study demonstrates the need for further research in children with AS in several areas. First, more research using standardized instruments is needed to clearly delineate differences in cognitive abilities as a function of genetic subtype in children with AS. Second, the relationship between autism and AS should be further explored in studies of children with AS. It will be important to determine whether or not there are any differences in the diagnosis of autism according to a child's genetic subtype of AS, as well as how a diagnosis of autism impacts cognitive, adaptive behavior, and language-based outcomes. Findings would also be enhanced in future studies that utilize standardized measures of expressive and receptive language skills, and how these relate to cognitive and adaptive behavior.

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