

Down Syndrome and Comorbid Autism-Spectrum Disorder: Characterization Using the Aberrant Behavior Checklist

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To report on the cognitive and behavioral attributes of 61 children with Down syndrome (DS) and autistic-spectrum disorder (ASD) according to DSM-IV criteria; to determine the utility of the aberrant behavior checklist (ABC) to characterize these subjects for research purposes; and to test the hypothesis that subjects with DS + ASD could be distinguished from their typical DS peers using the ABC. Cross-sectional design. Cases with DS + ASD (N = 61), comparison group of DS + stereotypy movement disorder (SMD) (N = 26) and typical DS controls without behavior problems (N = 44) were ascertained and enrolled sequentially upon presentation to a DS clinic at an academic medical center over a 10-year period from 1991 to 2001. All subjects underwent neurodevelopmental and medical evaluation, and standardized cognitive testing. The parents provided responses to standardized behavioral questionnaires. Cognitive function (IQ) differed markedly across the three groups. The Lethargy and Stereotypy subscales of the ABC were highly significant ($P < 0.001$) in distinguishing the three groups from one another. Within the ASD group differences were apparent by DSM-IV type on the Lethargy subscale, which reached significance, ANOVA ($F = 0.002$) and t -test (Autism > PDD, $P = 0.005$; PDD < CDD, $P = 0.002$). Using a multivariate regression model, the ABC scales alone explained 62% of variance of ASD outcome; addition of demographic variables explained up to 68% of the variance. There is good correlation between DSM-IV criteria for autism and subscales scores on the ABC in subjects with DS. This study demonstrates the feasibility of using the ABC to characterize the neuro-behavioral phenotype of a cohort of children

with trisomy 21 and ASD for ongoing research purposes. © 2005 Wiley-Liss, Inc.

KEY WORDS: pervasive developmental disorder; stereotypic movements; childhood disintegrative disorder; dual-diagnosis; aberrant behavior checklist; trisomy 21.

INTRODUCTION

Down syndrome (DS) is the most common genetic cause of moderate to severe mental retardation (IQ < 50) worldwide [Moser, 1985]. Like other genetically-based syndromes, the behavioral phenotype of DS demonstrates both group similarities and sometimes marked individual variation [Levinson et al., 1955; Clements et al., 1976; Rogers et al., 2001]. The majority of children with DS do not have a coexisting psychiatric or behavioral disorder [Gath and Gumley, 1986; Myers and Pueschel, 1991]. Of those with a comorbid disorder, severe behavioral disturbances such as autistic-spectrum disorders (ASDs) are considered uncommon, though important to recognize because of the prognostic significance.

The prevalence of ASD in persons with DS is estimated to be 5%–10% depending upon the criteria used and the method of ascertainment [Gath and Gumley, 1986; Gillberg et al., 1986; Lund, 1988; Myers and Pueschel, 1991; Ghaziuddin et al., 1992; Kent et al., 1999]. Given an estimated minimum prevalence of autism ~1/500 in the general population [Gurney et al., 2003], the expected prevalence of DS + autism (when conceptualized as discrete syndromes with different genetic risk-factors) would be {DS ~1:1,000} × {autism ~1:500} = 1 in 500,000. However, based upon an observed frequency of 5%–7%, we would predict a minimum prevalence rate of 1 in 20, [Kent et al., 1999] which is a 25-fold increase in risk compared to the general population. One epidemiological survey of autism in association with rare medical diseases conducted in the state of Utah revealed that trisomy 21 was the most common “rare disease” associated with autism [Ritvo et al., 1990]. A review of case reports and epidemiological surveys available in the medical literature indicates that no less than 73 persons with DS and comorbid ASD have been described [Wakabayashi, 1979; Coleman, 1986; Gath and Gumley, 1986; Gillberg et al., 1986; Bregman and Volkmar, 1988; Lund, 1988; Ritvo et al., 1990; Collacott et al., 1992; Ghaziuddin et al., 1992; Howlin et al., 1995; Ghaziuddin, 1997, 2000; Kent et al., 1998, 1999; Rasmussen et al., 2001]. From among these 3 population surveys and 12 case-series reports, 57 persons were under 21 years and 16 were over 21 years, and consisted of 50 males (73%), 18 females (27%), and 5 whose gender was not

Abbreviations: DS, Down syndrome; ASD, autistic-spectrum disorder; PDD, pervasive developmental disorder; CDD, childhood disintegrative disorder; SMD, stereotypy movement disorder; ALC, autistic-like condition; ABC, aberrant behavior checklist; DSM-IV, diagnostic and statistical manual IV.

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Received 7 May 2004; Accepted 28 December 2004

DOI 10.1002/ajmg.a.30622

given. An association between autism and severe cognitive impairment, as well as a preponderance of male subjects is apparent when reviewing these studies. Despite these reports, pediatric physicians and mental health providers may be reluctant to recognize or diagnose ASD in children with DS, often resulting in inappropriate educational placement for the child and unnecessary emotional hardship for their parents [Ghaziuddin et al., 1992; Howlin et al., 1995]. Arriving at this particular dual-diagnosis is often compromised by stereotyped notions about what it means to have DS, autism, or severe cognitive impairment. In addition, overall lower functional skills and associated maladaptive behaviors makes these children a particular challenge to evaluate. Furthermore, a pre-existing diagnosis of trisomy 21 probably contributes to their exclusion from existing research studies designed to investigate either idiopathic or "pure" Kanner-type autism.

It has been noted that ASD occurs with increased frequency in certain medical conditions [Gillberg and Coleman, 1996] with some variation in behavioral profile observed in specific genetic syndromes such as fragile X [Rogers et al., 2001; Kau et al., 2004]. Gillberg [1992] has urged for greater emphasis on studying different autism subgroups in order to explore the issue of neurobehavioral phenotype in association with specific medical and genetic conditions. In this regard, individuals with DS + ASD have been under-reported and inadequately studied with regard to their neurobehavioral phenotype and how it compares to either "typical" DS subjects or other autism syndromes. One of the most reliable and easiest to use behavioral instruments for the assessment of symptoms often associated with ASD in persons with severe cognitive impairment is the aberrant behavior checklist (ABC) [Aman et al., 1985a]. It has been used in children with mental retardation and comorbid psychiatric conditions to establish criterion validity among six categories of psychiatric diagnosis with good results [Rojahn and Helsel, 1991]. Additionally, the ABC has proven useful for measuring target symptoms associated with ASD in several clinical drug trials [Scahill and RUPP, 2002; Aman et al., 2004].

The purpose of this study then is to, (1) describe the cognitive and behavioral attributes of DS children with ASD; (2) to differentiate subjects with DS + ASD from typical DS subjects according DSM-IV criteria, and the ABC; and (3) determine the utility of using the ABC to further characterize this cohort for future research studies including pharmacological intervention.

SUBJECTS

Population

All subjects were recruited through the DS clinic at the Kennedy Krieger Institute between 1991–2001. ASD cases were ascertained and identified by the evaluating physician (gtc) from a larger group of children displaying an "autistic-like condition" (ALC) defined as "repetitive motor behaviors,

atypical attention, and unusual sensory responding" on examination. Very few of the children were on psychotropic medications at the time of evaluation. Medications when used did not appear to influence our diagnosis formulation. A child's estimated level of cognitive impairment was not used to exclude subjects from our study. Of the 471 initial visits by children ages 2–21 years during this 10 years period, 87 cases (18.5%) were identified as having an ALC. This notably high prevalence most likely indicates the referral pattern to our clinic. We excluded children whose behavior was better explained by a primary diagnosis of depression, obsessive-compulsive disorder, attention deficit hyperactivity disorder, tic disorder, oppositional-defiant, or disruptive disorder following a detailed history, medical evaluation, and review of DSM-IV criteria. We excluded several children whose socio-familial circumstances were significantly chaotic that it presented a source of confusion regarding their primary diagnosis. All of the typical DS controls, without behavioral problems, were selected at random from the DS Clinic roster. DS was confirmed in all cases by review of the karyotype report. Approximately 97% of subjects were found to have trisomy 21, the remainder having complete translocation of chromosome 21 (Table I).

Definitions

DS/ASD (cases) includes children with DS who met DSM-IV criteria for autism, pervasive developmental disorder (PDD), or childhood disintegrative disorder (CDD). All cases demonstrated symptom duration of at least 12 months. Following DSM-IV, subjects with autism manifested: at least two criteria from social impairment, and at least one each from communication impairment and repetitive/stereotyped patterns of behavior, with a minimum of six criteria met; and a history of abnormal function (not simply delay) or regression in at least one area prior to 36 months. Subjects with PDD manifested: at least one criteria from social impairment, communication impairment and repetitive/stereotyped patterns of behavior, with a minimum of four criteria met; and a history of abnormal function or regression in at least one area prior to 36 months. Subjects with CDD manifested: at least two criteria from social impairment, and one each from communication impairment and repetitive/stereotyped patterns of behavior; with a minimum of six criteria met; and neurobehavioral regression after 36 months, but not later than 10 years of age. Pre-morbid development prior to 36 months must have been "typical for toddlers with DS" as documented in early educational reports.

DS/stereotypic movement disorder (atypical comparison group) includes children who met DSM-IV criteria for this condition but failed to meet criteria for autism, PDD, or CDD.

DS/Typical (control group) includes children with minor or no concerns regarding their behavior as determined by parents and the examining physician. Occasionally we would encounter concerns about stubbornness, or motor activity level but not to the degree that a formal diagnosis was entertained.

TABLE I. Demographics

	ASD	SMD	Typical	All subjects	Test
Number	61	26	44	131	
Males (%)	49 (80.3%) ^a	21 (80.7%) ^a	26 (59%)	96 (72.7%)	Chi-square
Age years					ANOVA
Child	8.6 ± 4.4	7.6 ± 4.4	9.0 ± 4.7	8.6 ± 4.4	ns
Mother	30.4 ± 6.3	33.4 ± 5.8	29.1 ± 7.3	30.6 ± 6.6	ns
Father	33.3 ± 7.3	34.5 ± 5.9	32.7 ± 8.7	33.4 ± 7.5	ns
Trisomy 21	59/61 = 96.7%	25/26 = 96%	43/44 = 97.7%	127/131 = 96.9%	ns

^aASD versus Typical; SMD versus Typical $X^2 < 0.05$.

Identification

Those children presenting with an ALC were ascertained sequentially from all initial visits to the DS clinic by children 2–21 years, during the 10 years period under study (1991–2001).

Consent

Approval for this study was granted by the Johns Hopkins Medical Institutions Joint Committee on Clinical Investigation. Written informed consent was obtained from the parents or legal guardians of all children participating in this study. Verbal assent for cognitive testing was obtained from subjects whenever they were capable of understanding verbal explanation.

METHODS

DSM-IV Criteria

A clinical diagnoses and group assignment was made according to DSM-IV [APA, 1994] on the basis of all information obtained in connection with the various assessments, including behavior questionnaires, semi-structured neurodevelopmental evaluation, and observation during unstructured play or social settings. A single evaluator (gtc) was responsible for rating those with ALC using DSM-IV criteria. Prior to 1994 we used DSM-III-R [APA, 1987] criteria to categorize our subjects. This information was easily adapted into the DSM-IV format when it became available. For instance, in DSM-III-R there are six criteria available under Social impairment, which in DSM-IV have been collapsed into only four criteria but retaining the same type of information.

Cognitive Testing

The Bayley Scales of Infant Development Mental Scales [Bayley, 1969] was administered by a clinical psychologist to children whose abilities fell below the 2 years level ($N = 38$). The BSID is standardized for children from 1 to 30 months of age and yields a developmental age score which we used to derive a ratio DQ, score. A number of subjects were tested by a neurodevelopmental pediatrician ($N = 42$) using the clinical adaptive test/clinical linguistic auditory milestone scale known to be positively correlated with BSID scores in children with cognitive impairment [Hoon et al., 1993]. Ten subjects in total did not receive cognitive testing, ($ASD = 3$, $SMD = 5$ and $typical = 2$). The Stanford Binet-IV (SB-IV) [Thorndike et al., 1986] was given to children who exceeded the mental age of 2 years on the BSID ($N = 42$). This test is made up of 15 subtests within four broad areas: verbal reasoning, abstract/visual reasoning, quantitative reasoning, and short-term memory. A standard score is derived for each of these four areas with a single composite score with a mean of 100 (SD 16) is reported on our subjects. Throughout this article we prefer to use the term IQ when referring to comparisons which utilize both DQ and IQ scores.

Aberrant Behavior Checklist

The ABC was developed to measure a variety of maladaptive behaviors and their response to treatment in persons with moderate to profound mental retardation [Aman et al., 1985a]. The original ABC was also used by its authors to determine criterion validity in a population of persons with DS ($N = 159$) with good results [Aman et al., 1985b]. It has since been used in children and adolescents with dual diagnosis (mental retardation and psychiatric disorder) to establish criterion validity among six categories of psychiatric diagnosis, including autism, with good results [Rojahn and Helsel, 1991].

The ABC includes 58 items, assigned weighted scores 0–3 (3 indicating most severe), grouped into five symptom-clusters (irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech). Each of the symptom-clusters constitutes a distinct subscale, which is scored separately and considered independently from one another. Parents were asked to rate their child on these 58 attributes, during the past month, according to the checklist instructions.

Data Analysis

Descriptive statistics, means and standard deviations for measures are presented. ASD compared *t*-tests, stereotypy movement disorder (SMD), and the typical group ABC subscales scores in a pairwise fashion, controlling for multiple testing on the same data. For ASD subtypes, one-way ANOVAs between groups were conducted, then *t*-tests assuming unequal variance were run to determine differences between groups if the ANOVA was significant. To further explore the specific effect of IQ on results, the analyses were sequentially conducted on two restricted groups: moderate-to-severe mental retardation only (IQ 25–54; $N = 62$) and severe mental retardation only (IQ 25–39; $N = 32$). Other than this IQ cut-off no other exclusionary criteria were used. Univariate regressions predicted ASD for demographic and ABC subscales. Multivariate models using clinical variables (Model 1: age, sex, IQ), ABC subscales (Model 2), and both clinical and ABC subscale variables (Model 3) are presented to determine the significance of univariate predictors when controlling for other variables. Regression diagnostics included: (a) Cook's D to locate overly influential data points in univariate regressions; (b) Cook-Weisberg test to determine whether the models conformed to no error heteroskedasticity in multivariate regressions.

Ordered logistic regressions were used to estimate logistic models of the generated ordinal variable Typical-SMD-ASD labeled 0,1,2, respectively. This model allows for logistic modeling of an ordinal outcome and the actual values taken on by the variables (i.e., 0,1,2) are irrelevant except that larger values are assumed to correspond to "higher" outcomes. In the case of two outcomes the model becomes the logistic model. Also, the ordered logistic model using *j* categories assumes the odds ratio is constant for all categories. One can also derive probabilities for a given outcome (Typical, SMD, ASD) conditional on an independent variable(s) (age group, sex, ABC scores).

RESULTS

Demographics

We observed a significant over-representation of males in ASD ($49/61 = 80.3\%$) and SMD ($21/26 = 80.7\%$) groups compared to the typical ($26/44 = 59\%$) group ($P < 0.01$). There was no difference between groups for child's age (mean 8.6 years, $+4.4$), at time of evaluation, mother's age (mean 30.6 $+6.6$) or father's age (mean 33.4 $+7.5$) at the time of the child's birth (Table I).

DSM-IV Classification of Behavior Profiles

Among all subjects identified with an ALC ($N = 87$), autism was the most commonly made diagnosis, accounting for 41/87 (47%), followed by SMD, which was diagnosed in 26/87 (30%). CDD was diagnosed in 12/87 (14%) of subjects, and PDD was identified in 8/87 (9%).

Children classified as ASD satisfied an average of 3.5/4 (87.5%) of criteria under social impairment, compared to only 1.4/4 (35%) for the SMD group. The ASD group scored consistently high on criteria (a) "marked impairment in the use of multiple non-verbal behaviors" (98%); (b) "failure to develop

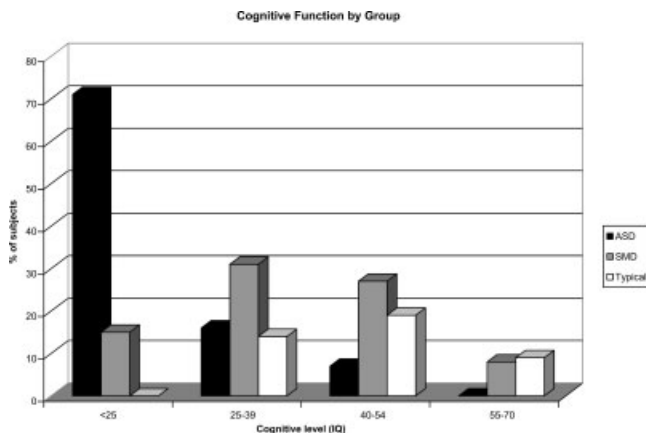


Fig. 1. Level of cognitive function by group assignment shows that for the ASD group 87% of subjects scored in the severe-profound (IQ 0–39) range, while 7% were in the moderate (IQ 40–54) range. In the stereotypy movement disorder (SMD) group 46% of subjects scored in the severe-profound (IQ 0–39) range, 27% of subjects were in the moderate (IQ 40–54) range, and 8% were in the mild (IQ 55–70) range. In the typical group 32% of subjects scored in the severe (IQ 25–54) range, 43% were in the moderate (IQ 40–54) range, and 20% were in the mild (IQ 55–70) range. (Mean IQ) ASD group (20.0 + 11.4); SMD group (38.2 + 11.9); Typical group (45.2 + 11.0). Group differences are significant by ANOVA $P < 0.00001$.

peer relations appropriate to developmental level” (84%); (c) “lack of spontaneous seeking to share enjoyment, interests or achievements with other people” (89%), and (d) “lack of social or emotional reciprocity” (79%).

Regarding communication skills, subjects with ASD scored consistently high on criteria (a) “total lack of, the development of spoken language—not accompanied by an attempt to compensate by alternative modes” (77%); (c) “stereotyped and repetitive use of language” (59%), and (d) “lack of varied, spontaneous make-believe play” (91%).

Using the criteria for stereotyped behavior showed that children classified as ASD satisfied an average of 3.1/4 (77.5%) of criteria compared to 2.5/4 (62.5%) for the SMD group. The ASD group scored consistently high on all criteria, notably (a) “preoccupation with one or more stereotyped and restricted patterns of interest” (98%); (b) “inflexible adherence to specific non-functional routines or rituals” (69%), and (c) “stereotyped and repetitive motor mannerisms” (98%).

Cognitive Function

No subject with ASD had mild (IQ 55–70) mental retardation, most (N = 54, 87%) were in the severe-profound (IQ 0–39) range of impairment, while few (N = 4) fell in the moderate range (IQ 40–54) (Fig. 1). The three ASD subjects who could

not be reliably tested were estimated to function in the severe-profound range of impairment. In contradistinction, no subjects with typical DS had profound mental retardation, most (N = 33, 75%) were in the moderate-severe range, and nine tested in the mild range of cognitive impairment, two subjects were untested. The subjects with SMD were seen at all levels of impairment, the majority (N = 15, 58%) were functioning in the moderate-severe range, while four tested in the profound and two in the mild range of impairment. Mean IQ x group is significant by ANOVA and is given in Figure 1.

Further characterization of the ASD group according to type (DSM-IV) reveals significant differences in cognitive function among the three types of ASD. The findings were as follows: autism, (N = 41, Male = 75%, IQ = 17.3 + 11), PDD, (N = 8, Male = 75%, IQ = 29.1 + 10.6), and CDD, (N = 12, Male = 83%, IQ = 20.6 + 6.9). The differences in IQ were significant by ANOVA (F = 0.01), and t-test (autism < PDD, $P = 0.008$, PDD > CDD, $P = 0.05$, autism vs. CDD, NS).

Aberrant Behavior Checklist

Each of the ABC subscales was increased in the ASD group compared to both the SMD and typical groups. Each of the three groups could be distinguished separately by ANOVA (F < 0.0001) on four of the subscales. As expected, these same four subscales were highly significant ($P < 0.0001$) in distinguishing between ASD and typical groups (Table II). Only the Inappropriate speech subscale was not significantly different ($P = 0.01$). The Lethargy and Stereotypy subscales were also highly significant ($P < 0.0001$) in distinguishing ASD and SMD groups, while the Irritability subscale showed a strong positive trend ($P = 0.006$). Neither the Hyperactivity ($P = 0.018$) or the Inappropriate speech ($P = 0.8$) subscale was helpful in distinguishing between the ASD and SMD groups. Compared to typical DS subjects, we observed consistently higher subscale scores in the SMD group. The Stereotypy ($P < 0.0001$), Lethargy ($P = 0.0008$), and Hyperactivity ($P = 0.002$) subscales proved to be significant, while the Irritability ($P = 0.036$) and Inappropriate speech ($P = 0.02$) subscales were not.

Characterization of the ASD group according to DSM-IV type revealed significant differences among the three types (autism, PDD, and CDD). The Irritability and Lethargy subscales differed most among the three types but reached significance only on the Lethargy scale, ANOVA (F = 0.002) and t-test (autism > PDD, $P = 0.005$, PDD < CDD, $P = 0.0002$) (Table III).

Subjects With Moderate to Severe Cognitive Impairment

To control for measured IQ, an analysis using only moderate-to-severe cognitively impaired subjects (IQ 25–54), was conducted. This analysis permitted us to examine for differences in behavior within a subgroup of subjects with similar cognitive function, which cannot be said for the larger group-

TABLE II. Aberrant Behavior Checklist (ABC)

Subscale	ASD	SMD	Typical	ANOVA	t-tests
Irritability	13.2 ± 9.3	7.4 ± 6.4	4.4 ± 4.4	F < 0.0001	a
Lethargy	18.1 ± 9.4	6.6 ± 5.5	2.5 ± 3.6	F < 0.0001	a,b,d
Stereotypy	12.5 ± 4.1	7.2 ± 3.1	0.5 ± 1.5	F < 0.0001	a,b,c
Hyperactivity	20.8 ± 10	15.4 ± 7.1	8.5 ± 8.7	F < 0.0001	a,e
Inappropriate speech	2.5 ± 3.0	2.3 ± 2.6	1.0 ± 1.7	F = 0.01	ns

ASD versus Typical: (a) $P < 0.0001$; ASD versus SMD: (b) $P < 0.0001$; SMD versus Typical: (c) $P < 0.0001$, (d) $P < 0.001$, (e) $P = 0.002$.

Post-hoc pairwise t-test statistical significance <0.003 after correcting for multiple comparisons using the Bonferroni procedure.

TABLE III. Aberrant Behavior Checklist (ABC) in Autistic-Spectrum Disorder (ASD) by DSM-IV Type

Subscale	Autism = 38	PDD = 8	CDD = 12	ANOVA	<i>t</i> -tests
Irritability	14.2 ± 10.1	8.5 ± 6.7	13.3 ± 7.7	F = 0.30	ns
Lethargy	18.6 ± 9.4	8.6 ± 5.8	22.8 ± 7.4	F = 0.002	a,b
Stereotypy	12.3 ± 4.2	11.2 ± 4.0	14.7 ± 3.4	F = 0.12	ns
Hyperactivity	20.7 ± 10.8	20.8 ± 10.0	21.3 ± 8.0	F = 0.98	ns
Inappropriate speech	2.0 ± 2.4	4.4 ± 5.0	2.4 ± 2.9	F = 0.12	ns

PDD versus CDD: (a) $P < 0.001$; Autism versus PDD: (b) $P = 0.005$.

Post-hoc pairwise *t*-test statistical significance < 0.003 after correcting for multiple comparisons using the Bonferroni procedure.

ings, thus permitting a more meaningful comparison of behavioral phenotype. This subgroup ($N = 62$) accounted for 47% of all study subjects. Significant differences were observed between ASD, SMD, and typical groups on the ABC composite, ANOVA ($F < 0.001$) and *t*-test for ASD > typical, and SMD > typical ($P < 0.0001$), but not between ASD and SMD groups ($P = 0.03$). Differences in the mean number of DSM-IV criteria met were significant for ASD > SMD, ANOVA ($F = 0.002$), and *t*-test ($P = 0.001$), (Table IV).

Each of the ABC subscales, with the exception of speech, were independently useful in distinguishing the ASD, SMD, and typical group, ANOVA ($F < 0.0001$) (Table V). In comparing the ASD and typical groups, the Irritability, Lethargy and Stereotypy subscales were highly significant ($P < 0.0001$), as were Hyperactivity and Inappropriate speech ($P = 0.0002$). In contrast, only the Lethargy subscale was helpful in distinguishing between the ASD and SMD groups ($P = 0.002$); suggesting that the Lethargy subscale is the most specific for predicting ASD in moderate-to-severely impaired children with DS and stereotypies. A comparison between SMD and typical groups also revealed differences on the Lethargy ($P = 0.05$) and Irritability ($P = 0.01$) subscales which approached significance, while each of the other three subscales were highly significant ($P < 0.001$). When subgroup analyses are limited only to subjects with severe cognitive impairment (IQ 25–39), accounting for 24% of all study subjects, the results did not vary.

Predicting Autistic-Spectrum Disorder

Given that maladaptive behavior forms a gradient of severity from typical to SMD to ASD, ordered logistic regressions were considered. When univariate ordered logistic regressions were used to predict ASD and SMD from demographic variables the odds ratio for gender (OR = 2.24) indicated that maleness confers an excess $2.24 \times$ risk of having SMD compared to typical controls, or an excess $2.24 \times$ risk of having ASD compared to SMD. Similarly, IQ score (OR = 0.88) confers a $1.14 \times$ (1/0.88) excess risk of having SMD compared to controls for every one IQ point decrease; likewise every one IQ point decrease confers a $1.14 \times$ excess risk of having ASD compared to SMD. Each of the ABC subscales taken separately

also confers an increased risk of SMD or ASD in the univariate model (Table VI).

Multivariate ordered logistic regressions were used to predict ASD from the same demographic variables and subscale scores mentioned above. Model 1: (age, sex, and IQ) was able to account for 33% (pseudo $R^2 = 0.33$) of the measured variance observed between ASD and typical groups. Model 2: (all five ABC subscales) were able to account for 62% (pseudo $R^2 = 0.62$) of the measured variance; whereas Model 3: (age, sex, IQ, and five ABC subscales) was able to account for 68% (pseudo $R^2 = 0.68$) of the measured variance between ASD and typical groups (Table VI). IQ is predictive of the typical-stereotypy-autism continuum but covaries enough with other predictors that in the full model it loses its significance. There is a non-significant trend for younger age to predict this continuum in multivariate Model 1. The Lethargy and Stereotypy subscales maintain their positive predictive power in both the univariate and multivariate models, when controlling for the other subscales, demographic variables, and IQ.

DISCUSSION

This study is the first of its kind to report on the diagnostic classification of a large cohort of children with DS with ASD, characterized using DSM-IV criteria, and the ABC. Of the 87 children identified with ALC, 61 were diagnosed with ASD and the remaining 26 had SMD. The 12.9% prevalence rate of ASD (61/471) from among the 471 children seen in our clinic during the 10 years period is higher than expected from other surveys (7%) [Kent et al., 1999], and most likely indicates a referral bias to our clinic as we have expressed an interest in evaluation and management of children with dual-diagnosis. We acknowledge evaluating a relatively greater number of subjects in the latter 5 years period (1996–2001) compared to the first 5 years (1991–1995). Although we believe this to represent a referral bias, an increase in the actual prevalence or detection of ASD cases occurring within the DS population cannot be excluded.

We found an over representation of male subjects with ASD in our sample (80%), which is in general agreement with prevalence estimates regarding autism in the general population and for DS/ASD cases previously reported in the published

TABLE IV. Scaled Scores in Moderate-Severe Cognitive Impairment

N	ASD	SMD	Typical	ANOVA	<i>t</i> -tests
	14	15	33		
IQ	36.7 ± 8.5	39.8 ± 6.7	40.6 ± 6.8	F = 0.228	ns
DSM IV criteria	8.3 ± 2.3	5.7 ± 1.2	NA	F = 0.002	a
ABC composite	58.4 ± 23.1	40.8 ± 16.2	15.2 ± 14.0	F < 0.001	b,c

ASD versus SMD: (a) $P = 0.001$; ASD versus Typical: (b) and SMD versus Typical: (c) $P < 0.0001$.

Post-hoc pairwise *t*-test statistical significance < 0.004 after correcting for multiple comparisons using the Bonferroni procedure.

TABLE V. Aberrant Behavior Checklist (ABC) in Moderate-Severe Cognitive Impairment

Subscale	ASD	SMD	Typical	ANOVA	t-tests
Irritability	11.2 ± 7.0	8.5 ± 7.0	3.7 ± 4.2	F < 0.0001	a
Lethargy	13.5 ± 8.6	5.3 ± 3.4	2.8 ± 3.9	F < 0.0001	a,c
Stereotypy	9.8 ± 4.8	7.3 ± 3.1	0.7 ± 1.7	F < 0.0001	a,d
Hyperactivity	19.6 ± 10.3	16.9 ± 7.8	7.3 ± 8.2	F < 0.0001	b,e
Inappropriate speech	4.2 ± 4.2	2.9 ± 2.7	0.6 ± 1.3	F = 0.018	b,e

ASD versus Typical: (a) $P < 0.0001$; (b) $P = 0.0002$; ASD versus SMD: (c) $P = 0.002$; SMD versus Typical: (d) $P < 0.0001$, (e) $P < 0.001$.

Post-hoc pairwise *t*-test statistical significance < 0.003 after correcting for multiple comparisons using the Bonferroni procedure.

literature (73%), [Wakabayashi, 1979; Coleman, 1986; Gath and Gumley, 1986; Gillberg et al., 1986; Bregman and Volkmar, 1988; Lund, 1988; Ritvo et al., 1990; Collacott et al., 1992; Ghaziuddin et al., 1992; Howlin et al., 1995; Ghaziuddin, 1997, 2000; Kent et al., 1998, 1999; Rasmussen et al., 2001]. Because of the design of our study, we were not able to determine the actual prevalence of males versus females with ASD in the larger DS population. However, our own experience, as well as the reports available in the literature, would suggest males are indeed disproportionately affected. The prevalence rate of SMD in our study was 5.5% (26/471). The over representation of male subjects with stereotypies but not ASD (80%) was somewhat unexpected, and has not been reported previously.

DSM-IV represents the most current consensus-derived system for typing the PDDs. Careful attention to development and social reciprocity criteria allows a distinction to be made between ASD and SMD. Children classified as ASD typically satisfied three or four criteria under social impairment, compared to only one or two for the SMD group. Interestingly, 11 of the SMD subjects had a moderate degree of social and relating impairment (two or more criteria met), which did not interfere significantly with social or academic function, thus excluding them from a clinical diagnosis of PDD or autism. However, these subjects sometimes demonstrated atypical social behaviors reminiscent of PDD or atypical autism. Further study of these subjects would be of interest regarding their prognosis and stability of the SMD diagnosis over time. Communication items were less helpful for distinguishing differences between ASD and SMD, perhaps because of the poor expressive language skills common in DS. Three of the four items listed under communication impairment emphasize spoken language skills, which would tend to penalize all children with DS especially lower functioning individuals. Subjects with ASD however, demonstrated marked impairment in non-verbal communication and symbolic play beyond that expected for their mental age. Stereotypies were frequent and intense in both the ASD and SMD groups. Children classified as ASD satisfied an average of three stereotypy criteria compared to two or three for the SMD group.

Children with DS classified as CDD present a special nosologic challenge in our study. Typically, CDD, which is thought to be quite rare, is often excluded from the early-onset autism-spectrum disorders for research purposes, although the rationale for doing so has been questioned [Hendry, 2000]. Our decision to include CDD under the umbrella of ASD relates to several factors, including its apparent increased prevalence in DS and our ability to exclude coexisting medical conditions around the time of presentation.

One of the limitations of this study is that comprehensive measures of cognitive function in populations such as ours are notoriously difficult to perform even in the best of circumstances. Generalized low function and maladaptive behaviors make this so, and are probably more significant variables than any inconsistency introduced by using different test instru-

ments such as the Stanford-Binet IV in higher functioning subjects, and the Bayley Scales of Infant Development in lower functioning children. A visual-performance based measure, which does not unduly penalize children for language-based impairments might be a more suitable estimate of cognition to serve as a basis for comparison among subjects with DS. Thus, the subjects in our cohort may have been assigned an IQ or DQ somewhat lower than expected. These cognitive differences may confound the reported differences in behavioral profile between groups which are not fully addressed by the multivariate analysis. Hence, comparing behavioral differences between groups, which are more closely matched on IQ takes on added importance. Further investigation of cognition and its contribution to various aspects of the neurobehavioral phenotype should also be the subject of future study.

Our finding of a negative correlation between the severity of autistic behaviors and cognition in DS subjects is not unexpected. Bartak and Rutter commented on this relationship in their seminal study describing differences between normally intelligent and mentally retarded autistic children [Bartak and Rutter, 1976]. However, our data suggests that most subjects with ASD (87%) are functioning in the severe-profound range, while those with typical behaviors are more likely to be in the mild-moderate range (63%). Such a striking difference in the distribution of cognitive impairment may confound the statistical analysis of behavior measures between groups as presented in this study. Interestingly, subjects with SMD appear to occupy an intermediate position between these two extremes both cognitively and behaviorally. A question thus arises as to the nature of the relationship between cognitive and behavioral function in children with DS. While it is accepted that low cognition generally increases the risk for developing autistic behaviors, it is plausible that the relationship is not exactly causal; rather both severe cognitive and behavioral impairment represent two separate outcomes each sharing common underlying neurobiological mechanisms. The most significant finding in this regard is the clear difference between ASD, SMD, and typical neurobehavioral phenotypes in the presence of moderate-severe cognitive impairment. Severe cognitive impairment can and does occur in children with DS who are sociable and have functional communication skills [Wing and Gould, 1979; Waterhouse et al., 1996]. By further characterizing this group, without atypical behavior, we corroborate and extend the findings of Wing and Gould who described 27 of 28 subjects with DS in their study as being sociable [Wing and Gould, 1979].

The ASD subjects in our study had significantly increased ABC subscale scores compared to typical controls and SMD, except for the Inappropriate speech subscale. When comparing subjects with ASD versus SMD the Lethargy and Stereotypy scales were most helpful, Irritability, and Hyperactivity somewhat helpful, while the Inappropriate speech scale was not helpful in distinguishing the groups. The ASD group scored consistently higher than the SMD group on most subscales but reached statistical significance only on the Lethargy subscale.

TABLE VI. Ordered Logistic Regressions Predicting ASD, Stereotypy Movement Disorder (SMD) or Typical by Age, Sex, IQ, and Aberrant Behavior Checklist (ABC)

Variable	Univariate regression (odds ratio)	Multivariate Model 1 (odds ratio)	Multivariate Model 2 (odds ratio)	Multivariate Model 3 (odds ratio)
Age	0.99	0.93 (t)		0.90
Sex	2.24 ^a	1.87		0.59
IQ	0.88 ^c	0.88 ^c		0.95 (t)
ABC Irritability	1.17 ^c		0.97	0.95
ABC Lethargy	1.33 ^c		1.19 ^b	1.29 ^b
ABC Stereotypy	1.80 ^c		1.65 ^c	1.55 ^c
ABC Hyperactivity	1.14 ^c		1.07	1.07
ABC Speech	0.62 ^a		0.93	0.93
Pseudo-R ²		0.33	0.62	0.67

^a $P < 0.05$.^b $P < 0.01$.^c $P < 0.001$, (t) $0.05 < P < 0.10$.

Interestingly, the ASD group was also rated higher on the Hyperactive subscale which measures attention, activity, and oppositionality, characteristics of some of our ASD subjects. It is difficult for us to reconcile this apparent incongruency of being both lethargic (eg., socially-emotionally withdrawn), yet hyperactive as characteristic of all our ASD subjects. Thus, we were able to identify among the ASD subjects a subgroup rated primarily as lethargic without hyperactivity ($N = 13$), a second group who are primarily hyperactive without lethargy ($N = 14$), and a third group who scored above the mean for the entire ASD group on both lethargy and hyperactivity ($N = 17$). When the same data are analyzed according to DSM-IV type it is apparent that those classified as PDD are less socially and emotionally withdrawn or "lethargic" compared to subjects with autism or CDD, despite a similar degree of hyperactivity in all three types. Thus, these putative subgroups appear to have some relationship to DSM-IV type.

Among those subjects with moderate-severe cognitive impairment each of the three groups differ significantly using DSM-IV criteria and the ABC, as the ABC subscale scores remained significantly lower in the typical group compared to either ASD or SMD groups. Comparison between ASD and SMD groups revealed consistently higher scores in the ASD group on each of the subscales, with Lethargy and Stereotypy being the most significant. This comparison most accurately captures the magnitude of behavioral difference between the groups because the distribution of cognitive impairment is held relatively constant, and is generally consistent with our findings in the larger (non-IQ matched) groups.

Because subjects with SMD also had significantly increased scores on each of the ABC subscales we conclude that these children differ in important ways from both ASD and typical DS subjects on domains other than stereotypy, particularly attention and social withdrawal. If one assumes that the relationship between typical-SMD-ASD is ordered, and that the risk is the same when going from typical to SMD, or SMD to ASD, then the notion that children with SMD are "behaviorally atypical" but not quite autistic is supported by multivariate ordered logistic Models 2 and 3; as well as the cognitive testing. These findings raise questions about the neurobiological basis and apparent vulnerability of neuronal circuits which modulate stereotypy, social, and attentional function in young males with DS.

The original factor structure of the ABC has been cross-validated in persons with moderate to profound mental retardation, [Bihm and Poindexter, 1991], and it has been used to assess children with dual diagnosis (mental retardation and autism) with good results [Rojahn and Helse, 1991]. More recently, it has proven useful for measuring target symptoms associated with ASD in clinical drug trials [Scahill

and RUPP, 2002; Aman et al., 2004]. Our findings suggest that the ABC may be an especially useful assessment tool for subgrouping children with DS and comorbid psychiatric conditions, and for measuring the outcome of drug intervention studies.

Diagnostic Issues

Given the information generated by this study it maybe helpful to ask if an additional diagnosis of autism, PDD, or CDD is clinically useful or even necessary in children with DS?

Currently we reserve clinical diagnosis of DS + ASD for those children meeting DSM-IV criteria for autism, PDD, or CDD only. Rigorous application of existing DSM-IV criteria and multiple, preferably extended observations in different settings remains critical for diagnostic purposes. We caution against over reliance upon standardized rating scales to make the diagnosis of ASD. It is our suggestion that DS children with late-onset regression warrant inclusion under CDD at this time if the criteria that development be "apparently normal" for the first 2 years of life, is reformulated as "apparently normal for DS." Because of the marked deterioration in cognitive and adaptive skills in addition to new-onset maladaptive behaviors accompanying a regression, we believe it is paramount that a diagnosis of CDD or "late-onset autism" be made in order to acknowledge the child's primary (most impairing) diagnosis. Nosology notwithstanding, there is an apparent increased prevalence of CDD in children with DS which has received little mention in the available literature (in preparation). Contrawise, we have not observed DS individuals with coexisting Asperger's syndrome

It is a matter of some debate whether a child with profound cognitive impairment ($IQ < 25$), without neurodevelopmental regression should be given an additional diagnoses of ASD even when all DSM-IV criteria are met, as many clinicians would surmise that the behavioral disturbance is inextricably linked to the cognitive impairment. In practical terms, it also remains unclear to what degree state-of-the-art educational or communicative interventions will benefit such individuals.

CONCLUSION

Using widely available clinical assessment tools, we have been able to distinguish distinct neurobehavioral phenotypes among young persons who share the most common chromosomal syndrome, trisomy 21. Despite documentation of variability in behavioral manifestation within a genetic syndrome [Rogers et al., 2001; Kau et al., 2004], it is frequently regarded that individuals with the same syndrome must share a common behavioral phenotype [Moldavsky et al., 2001]. Since

behavioral variability has been demonstrated for single-gene disorders, and microdeletion syndromes, the concept of individual variation becomes even more critical when considering cases of chromosomal aneuploidy like trisomy 21 [Levinson et al., 1955; Clements et al., 1976] with several hundred genes at dosage imbalance [Gardiner et al., 2004]. There is a continued need for studies that examine phenotypic variation in DS utilizing contemporary neurobiological and neuropsychological models, [Capone, 2001] which can also account for other genetic and familial factors. Clinically, there remains an enormous need to establish objective indicators of neurobehavioral and psychiatric comorbidity and treatment outcomes in persons with DS specifically.

From the perspective of parents struggling to understand why their child exhibits atypical behavior or reduced potential for social and language-based learning, having a specific diagnosis of ASD is critically important. They will after all, need to provide nurturance, guidance, and advocacy for their child throughout their life. The same is true for psychologists and school personnel who need to create a realistic curriculum, functional communication program and behavior management strategies.

ACKNOWLEDGMENTS

The authors thank each of the children and their families who made this work possible. We also thank Margaret Pulsifer, PhD for many helpful suggestions in the early stages of this project. W.E.K. receives partial support from MH067092. M.A.G. receives partial support from K23MH066284.

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