

# Down Syndrome and co-morbid Autism-spectrum disorder: Characterization using the Aberrant Behavior Checklist

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**Abbreviations:** Down syndrome (DS), Autistic spectrum disorder (ASD), Pervasive developmental disorder (PDD), Childhood disintegrative disorder (CDD), Stereotypy movement disorder (SMD), Autistic-like condition (ALC), Aberrant Behavior Checklist (ABC), Diagnostic & Statistical Manual IV (DSM-IV)

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## Abstract

**Objectives:** 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.

**Study design:** 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 1991-2001. All subjects underwent neurodevelopmental and medical evaluation, and standardized cognitive testing. The parents provided responses to standardized behavioral questionnaires.

**Results:** Cognitive function (IQ) differed markedly across the 3 groups. The Lethargy and Stereotypy subscales of the ABC were highly significant ( $P < 0.001$ ) in distinguishing the 3 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.

**Conclusions:** 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 neurobehavioral phenotype of a cohort of children with trisomy 21 and ASD for ongoing research purposes.

**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 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, Friedman et al. 1955; Clements, Bates et al. 1976; Rogers, Wehner 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 (ASD) 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, Persson et al. 1986; Lund 1988; Myers and Pueschel 1991; Ghaziuddin, Tsai et al. 1992; Kent, Evans et al. 1999). Given an estimated minimum prevalence of autism  $\sim 1/500$  in the general population (Gurney, Fritz et al. 2003), the expected prevalence of DS + autism (when conceptualized as discrete syndromes with different genetic risk-factors) would be  $\{DS \sim 1:1000\} \times \{\text{autism} \sim 1:500\} = 1$  in 500,000. However, based upon an observed frequency of 5-7%, we would predict a minimum prevalence rate of 1 in 20, (Kent, Evans 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, Mason-Brothers 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, Persson et al. 1986; Bregman and Volkmar 1988; Lund 1988; Ritvo, Mason-Brothers et al. 1990; Collacott, Cooper et al. 1992; Ghaziuddin, Tsai et al. 1992; Howlin, Wing et al. 1995; Ghaziuddin 1997; Kent, Perry et al. 1998; Kent, Evans et al. 1999; Ghaziuddin 2000; Rasmussen, Borjesson 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 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, Tsai et al. 1992; Howlin, Wing 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 preexisting diagnosis of trisomy 21 probably

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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, Wehner et al. 2001) (Kau, Tierney et al. 2004) Gillberg 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 (Gillberg 1992). 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, Singh et al. 1985). 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, Novotny 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 Down Syndrome 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 year 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

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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 Down Syndrome 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 1**).

## **Definitions**

*DS/Autistic Spectrum Disorder (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 2 criteria from social impairment, and at least 1 each from communication impairment and repetitive/stereotyped patterns of behavior, with a minimum of 6 criteria met; and a history of abnormal function (not simply delay) or regression in at least 1 area prior to 36 months. Subjects with *PDD* manifested: at least 1 criteria from social impairment, communication impairment and repetitive/stereotyped patterns of behavior, with a minimum of 4 criteria met; and a history of abnormal function or regression in at least 1 area prior to 36 months. Subjects with *CDD* manifested: at least 2 criteria from social impairment, and 1 each from communication impairment and repetitive/stereotyped patterns of behavior; with a minimum of 6 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.

## **Identification**

Those children presenting with an ALC were ascertained sequentially from all initial visits to the Down Syndrome Clinic by children 2-21 years, during the 10 year 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.

### **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 6 criteria available under *Social impairment*, which in DSM-IV have been collapsed into only 4 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 two year level (N= 38). The BSID is standardized for children from 1-30 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, Pulsifer 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, Hagen 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 fifteen 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 Aberrant Behavior Checklist (ABC) was developed to measure a variety of maladaptive behaviors and their response to treatment in persons with moderate to profound mental retardation (Aman, Singh et al. 1985). 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, Singh et al. 1985). 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 to 3 (3 indicating most severe),

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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. T-tests compared ASD, 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 overrepresentation 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,  $\pm 4.4$ ), at time of evaluation, mother's age (mean  $30.6 \pm 6.6$ ) or father's age (mean  $33.4 \pm 7.5$ ) at the time of the child's birth (**Table 1**).

### 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 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) (**Figure 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 =  $17.3 \pm 11$ ), PDD, (N = 8, Male = 75%, IQ =  $29.1 \pm 10.6$ ) and CDD, (N = 12, Male = 83%, IQ =  $20.6 \pm 6.9$ ). 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 v 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 3 groups could be distinguished separately by ANOVA ( $F < 0.0001$ ) on 4 of the subscales. As expected, these same 4 subscales were highly significant ( $P < 0.0001$ ) in distinguishing between ASD and typical groups (**Table 2**). 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 3 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 3**).

### **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 groupings, 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 ( $F < 0.0001$ ) 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 ( $F < 0.0001$ ) and t-Test ( $P = 0.0007$ ), (**Table 4**).

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 5**). 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 ( $P =$

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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 2.24x risk of having SMD compared to typical controls, or an excess 2.24x risk of having ASD compared to SMD. Similarly, IQ score ( $OR = 0.88$ ) confers a 1.14x ( $1/0.88$ ) excess risk of having SMD compared to controls for every 1 IQ point decrease; likewise every 1 IQ point decrease confers a 1.14x 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 6**).

Multivariate ordered logistic regressions were used to predict ASD from the same demographic variables and subscale scores mentioned above. Model 1: (age, sex, 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 6**). 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 Irritability 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 Aberrant Behavior Checklist. 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 year period is higher than expected from other surveys (7%) (Kent, Evans 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 year period (1996-2001) compared to the first 5 years (1991-1995). Although we believe this to represent a referral bias,

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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 literature (73%), (Wakabayashi 1979; Coleman 1986; Gath and Gumley 1986; Gillberg, Persson et al. 1986; Bregman and Volkmar 1988; Lund 1988; Ritvo, Mason-Brothers et al. 1990; Collacott, Cooper et al. 1992; Ghaziuddin, Tsai et al. 1992; Howlin, Wing et al. 1995; Ghaziuddin 1997; Kent, Perry et al. 1998; Kent, Evans et al. 1999; Ghaziuddin 2000; Rasmussen, Borjesson et al. 2001). Because of the design of our study we were not able to determine the actual prevalence of males vs. 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 pervasive developmental disorders. Careful attention to development and social reciprocity criteria allows a distinction to be made between ASD and SMD. Children classified as ASD typically satisfied 3 or 4 criteria under social impairment, compared to only 1 or 2 for the SMD group. Interestingly, eleven 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 4 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 3 stereotypy criteria compared to 2 or 3 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 co-existing medical conditions around the time of presentation.

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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 instruments 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, Morriss 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 vs 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

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consistently higher than the SMD group on most subscales but reached statistical significance only on the Lethargy subscale. 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 incongruity 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 3 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 3 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 Helsel 1991). More recently, it has proven useful for measuring target symptoms associated with ASD in clinical drug trials (Scahill and RUPP 2002; Aman, Novotny 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 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 two 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, Wehner et al. 2001; Kau, Tierney et al. 2004), it is frequently regarded that individuals with the same syndrome must share a common behavioral phenotype (Moldavsky, Lev 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, Friedman et al. 1955; Clements, Bates et al. 1976) with several hundred genes at dosage imbalance (Gardiner, Davisson 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

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need to establish objective indicators of neurobehavioral and psychiatric co-morbidity 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, or functional communication program and behavior management strategies.

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