Pattern of Diagnosis and Co-occurring Symptoms in Adopted Children With Autism Spectrum Disorder

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abstract

OBJECTIVES: To determine whether adopted children with autism spectrum disorder (ASD) differ from the general ASD population in terms of diagnosis, internalizing and externalizing behaviors, sleep problems, and medications.

METHODS: We studied 163 adoptees in the Autism Speaks Autism Treatment Network (ATN) in comparison with 5624 nonadopted ATN participants (aged 1.5–17.6 years; mean [SD] = 6.2 [3.4] years). Gender, age, race, ethnicity, IQ, and categorical *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, ASD diagnosis were tested for differences by group (adopted versus nonadopted) by using independent-samples *t* tests for continuous variables and Fisher's exact tests for categorical variables. Logistic or linear regression models were used to examine the association between adoption status and several outcome variables, after controlling for covariates.

RESULTS: After controlling for demographics and diagnosis, there were significant differences in group characteristics, including greater propensity for externalizing behavior ($P < .001$), internalizing behavior ($P = .001$), and sleep problems ($P < .001$) in the adopted population. Adoptees were also prescribed psychotropic medications ($P < .001$) more often than the nonadoptees. Adoptees received a diagnosis of pervasive developmental disorder–not otherwise specified significantly more frequently than controls (odds ratio = 1.8; CI = 1.3–2.5; $P < .001$), despite no significant difference in symptoms on standardized measures.

CONCLUSIONS: These results suggest that the population of adopted children with ASD differs from the general ASD population both with regard to diagnostic subtype and co-occurring behavioral problems. Future research should evaluate the contributions of specific factors associated with adoption such as biological family history, pregnancy history, early childhood experience, and age at adoption.

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The relationship between risk of autism spectrum disorder (ASD) and adoption has not been extensively investigated despite data revealing neurodevelopmental risks associated with adoption. A variety of risk factors are more likely to have been experienced by adopted children, such as prenatal drug exposure, early abuse or neglect, and institutional care.[1–5] The risks associated with adoption range from early developmental issues, such as failure to thrive or general developmental delay, to symptoms emerging later in childhood or adolescence, including affective or attachment problems. These risks and outcomes of adoption overlap with characteristics of ASD; however, very little research has evaluated the relationship between the 2 populations.

Although a large majority of adopted children develop typically,[1,6] adopted children as a group have an increased risk of externalizing behaviors such as aggression, hyperactivity, and oppositionality.[7] In support of this observation, a Swedish study found that adopted children had higher rates of prescribed attention-deficit/hyperactivity disorder (ADHD) medications in comparison with nonadopted children.[1,8] Hawk and McCall[9] used the Child Behavior Checklist (CBCL) to compare postinstitutionalized adoptees with nonadopted and noninstitutionalized adoptees and found that postinstitutionalized adopted children have higher levels of externalizing and attention problems than nonadopted children or noninstitutionalized adoptees. Even adopted children who initially adapt positively may show patterns of later emerging internalizing, externalizing, and behavior problems.

Along with higher levels of externalizing behavior, adoptees are more likely to have higher levels of internalizing problems.[1] The Adoption Meta-analysis Project is a compilation of results examining adopted children's adjustment and development. In the Adoption Meta-analysis Project, more behavioral problems were evident in adoption cases than in nonadopted controls, with international adoptees showing the greatest increases in both externalizing and internalizing behaviors.[10] Older postinstitutionalized children showed higher levels of internalizing problems than did younger postinstitutionalized children. Also, children adopted later had more problems with internalizing than children adopted at a younger age.[9] For example, the English Romanian Adoption (ERA) Study observed a significant increase in emotional problems from age 6 to age 11 in previously institutionalized children.[11] An analysis of the National Epidemiologic Survey on Alcohol and Related Conditions compared adopted with nonadopted individuals and found that adoptees had increased odds of developing a mood disorder, anxiety disorder, major depressive disorder, and generalized anxiety disorder.[12] Studies in internationally adopted children showed sleep problems as a main adjustment difficulty, even in the absence of developmental problems.[1]

Despite an association between adoption and developmental problems, minimal data have allowed an explicit assessment of the relationship between adoption and neurodevelopmental disorders such as ASD. The primary study that evaluated the intersection between adoption and ASD is the ERA study by Rutter et al.[13] This prospective longitudinal study evaluated the effects of early deprivation in 165 Romanian children adopted into the United Kingdom. Longitudinal observations of the adoptees from arrival through 4, 6, 11, and 15 years identified an array of features described as "quasi-autism" seen in 11 children at age 4 (6.7%). Quasi-autism was defined as "a pattern that showed autistic-like features (particularly, intense circumscribed interests) but which differed from 'ordinary' autism in greater social interest and flexibility."[13] Despite these relative social strengths in comparison with typical ASD, these adoptees showed difficulties in social awareness and reciprocity, empathy, interpersonal boundaries, and communication.[13] Preoccupations with sensations and intense circumscribed interests were also prominent, but these children did not show the stereotyped motor behaviors often observed in ASD. Within the ERA study, quasi-autism symptoms often manifested well after adoption. By age 11 years, 12 of the available 141 institutionalized children (8.5%) with an IQ >50 fit the "quasi-autism" profile. An additional 12 children (8.5%) had some ASD symptoms but fell short of diagnosis, largely due to better social and communication function.[14,15]

A myriad of factors moderate the associated risks within the population of adopted children, including age at adoption, previous institutionalization, and international versus domestic adoption.[1,9,10,16–18] Importantly, early intervention, including adoption, may prevent later cognitive and emotional problems in institutionalized children. In the Bucharest Early Invention Study, institutionalized children were randomly assigned to either remain in an institution or receive foster care. Children who remained in institutions had markedly lower cognitive outcomes than those placed in foster care.[1]

Direct parallels should not be drawn between the ERA and Bucharest Early Intervention populations and the general

population of adoptees within the United States and Canada, where the Autism Speaks Autism Treatment Network (ATN) is based. The majority of international adoptees can be expected to have spent some time in an institutional setting,[6] but these settings are highly variable and should not be assumed to represent the deprivation described in Eastern European orphanages soon after the fall of communism. Most domestic adoptees in the United States and Canada would not have experienced institutional care before adoption.[19]

On the basis of the complex pattern of increased behavioral and cognitive problems in the general adopted population and the observed patterns of quasi-autism in the ERA study, we hypothesized that atypical, complex patterns of ASD would be more likely in the adopted population. Specifically, we expected a higher rate of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV), pervasive developmental disorder–not otherwise specified (PDD-NOS) in adopted children in comparison with nonadopted children within the ATN. Furthermore, on the basis of the higher prevalence of these behavioral problems in adopted populations, we hypothesized that adopted children with ASD would also present with more internalizing, externalizing, and sleep problems than nonadopted ASD populations.

METHODS

Participants

The data were gathered and analyzed under an institutional review board umbrella protocol used by the ATN/Autism Intervention Research Network on Physical Health Network's Data Coordinating Center at Massachusetts General Hospital. The ATN data registry includes children and adolescents with ASD across 17 sites in the United States and Canada. Inclusion in the database required a participant to meet the DSM-IV[20] diagnostic criteria for autistic disorder, Asperger syndrome, or PDD-NOS on the basis of a clinical assessment including the Autism Diagnostic Observation Schedule (ADOS).[21] Data from the initial (baseline) ATN visit were used to examine the relationship between adoption status, demographic, and clinical variables. The data were analyzed from a total sample of 5787 individuals who had gender, age at enrollment, and ethnicity information available and excluded those with an ASD residual state diagnosis.

Measures

Adoption Status

Adoption status was determined by parent indication of their relationship to the patient on the Parent Assessment open-field question. If a parent used a phrase that included the stem "adopt" (ie, "adopted," "adoptive," etc), the individual was included in the adopted group. All other participants constituted the comparison group.

Cognitive Ability

Children's cognitive functioning was assessed by using the Stanford Binet,[22] Mullen Scales of Early Learning (Early Learning Composite),[23] Differential Abilities Scale-II,[24] Wechsler Intelligence Scale for Children (WISC-IV Full Scale),[25] Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III),[26] or the Bayley (Cognitive composite),[27] depending on the ATN site's preference, scale availability, and child's age and language ability.

Diagnosis

ASD diagnosis was drawn from the DSM-IV Symptom Checklist and the Diagnoses and Problems Clinician Report Form (DX1). On the DX1 the clinician could diagnosis an individual with "Asperger's DO," "Autism-current/active state," "Autism-residual state," or "PDD-NOS." The DSM-IV Symptom Checklist allowed the clinician to indicate "Autism," "Asperger's," or "PDD/NOS." Occurrence of PDD-NOS was collected from these assessments. The DSM-IV Symptom Checklist was also used to analyze differences in individual autism symptoms between groups.

Behavioral Problems

The Health and Mental Health History Survey was used to assess participants' lifetime prevalence of medical and psychiatric problems, as well as family history of developmental and psychiatric disorders. On a list of 29 items, caregivers responded "yes," "no," or "unsure" to every item, indicating either a current or past diagnosis. The assessment was used to measure rates of ADHD in each group.

The CBCL[28] is a validated, age-based caregiver questionnaire measuring a variety of internalizing and externalizing behaviors. In these analyses, we used the versions intended for children aged 1.5 to 5 years and 6 to 18 years. The initial analysis examined the Externalizing and Internalizing subscales, with follow-up analyses of narrower subscales to further characterize observed differences between the groups.

At entry into the ATN, clinicians indicate diagnoses or observations for a number of problems on the Diagnoses and Problems Clinician Report Form. Items are grouped into broad categories including gastroenterology, nutrition, neurologic, psychiatric, sleep, speech, skin conditions, and other. Items endorsed under ADHD or Separation Anxiety were included for analysis of ADHD and anxiety rates. Medications were also recorded and categorized

TABLE 1 Demographic Comparison Between Adoptees With ASD and Nonadoptees With ASD

	Nonadoptees With ASD (n = 5624)	Adoptees With ASD (n = 163)	P
Age at enrollment, mean (SD), y	6.2 (3.4)	7.9 (3.8)	<.001
Gender, %			<.001
Male	84.1	72.4	
Female	15.9	27.6	
Race, %			.041
Nonwhite/-Caucasian	19.5	25.8	
White/Caucasian	80.5	74.2	
Ethnicity, %			.317
Hispanic/Latino	8.3	10.4	
Non-Hispanic/-Latino	91.7	89.6	
IQ, mean (SD)	75.9 (24.7)	78.0 (22.1)	.288

Total N = 5787, except for IQ (total N = 4345; n = 4210 nonadoptees with ASD and 135 adoptees with ASD).

by both disorder and medication type. From this measure we collected rates of psychotropic medications, as well as medications for ADHD, aggression, anxiety, and sleep.

Sleep Habits and Problems

The Children's Sleep Habits Questionnaire (CSHQ) was used to indicate the presence of sleep problems. The CSHQ is a validated measure in the ASD population[29,30] and assesses various sleep problems. Questions are answered on a 3-point scale ("rarely," "sometimes," "usually"), and items rated as "sometimes" or "usually" were used to endorse sleep problems in the current study. In addition to the CSHQ, sleep problems were measured from selected variables from other assessments. A "yes" to "sleep issues" on the Lead Autism Specialist Assessment, "sleep problems" on the Parent Survey, or "sleep issues/concern" on the Diagnosis and Treatment Form–Parent Report were categorized as a sleep problem.

Statistical Methods

Demographic and individual characteristics, including categorical ASD diagnosis, gender, age, race, ethnicity, and IQ, were tested for differences by group (adopted versus nonadopted) by using independent-samples t tests for continuous variables and Fisher's exact tests for categorical variables. For any continuous variables that were tested by using t tests, the folded F test for equality of variances was conducted first. If a variable passed this test, then the pooled t test results, assuming equal variances, are reported. If a variable did not pass this test, then the Satterthwaite t test results, assuming unequal variances, are reported. Only age at enrollment and IQ did not pass the folded F test for equality of variances. Variables that differed significantly at a threshold of $P <$ .05 were included in subsequent logistic or linear regression models. The primary hypothesis was that PDD-NOS would be more commonly diagnosed in the adopted population. The secondary hypotheses were that externalizing behavior, internalizing behavior, sleep problems, and psychotropic medication prescriptions would be more common in the adopted population. Subsequent analyses of subcategories ofDiagnostic and Statistical Manual of Mental Disorders, Fourth Edition, symptoms, co-occurring behaviors, or specific medications were viewed as exploratory. The α levels of 0.05, 0.01, and 0.001 were used to assess the primary, secondary, and exploratory hypotheses, respectively. Adjusted logistic or linear regression models were used to examine the associations between these variables and adopted status. Data analyses were conducted using by SAS software, version 9.4, of the SAS System for Windows (SAS Institute, Cary, NC).

RESULTS

A total of 163 parents indicated that their child was adopted (2.8%), and 5624 parents did not (97.2%). Overall, participants ranged in age from 1 year, 6 months, to 17 years, 6 months (mean [SD] = 6.2 [3.4] years). The total study sample consisted of 83.8% boys (16.2% girls) and most were white (80.4%). The adopted group had a significantly higher percentage of female participants (27.6%) than the nonadopted participants (15.9%). The adopted population also had more diversity in terms of race (Table 1), with a higher percentage of Asians (9.8% adopted versus 5.1% nonadopted). Importantly, given that many Asian adoptees are female, the higher proportion of girls among adopted children with ASD compared with girls in the nonadopted ASD group was still present when adoptees of Asian origin were removed from the analysis (girls: 24.5%; boys: 75.5%; $P <$ .001). Adopted participants were significantly older (mean [SD] = 7.9 [3.8] years) at time of ATN enrollment than the control participants (mean [SD] = 6.2 [3.4] years; $P <$ .001). Neurologic history or language delay did not appear to explain these findings because a significant difference was not found between adoptees' and nonadoptees' history of seizures/seizure medications (P = .134) or in general language delay (P = .221). Age, gender, and race were included as covariates in subsequent corrected analyses.

The adopted group showed higher rates of PDD-NOS diagnosis (39.3% vs 26.4% in the nonadopted group; odds ratio [OR] = 1.8; [CI] = 1.3–2.5;

TABLE 2 Comparison of CBCL T-Scores Between Adoptees With ASD and Nonadoptees With ASD

Variable	Nonadoptees With ASD			Adoptees With ASD					
	n	Mean	SD	*n*	Mean	SD	*P*	Maximum Likelihood Estimate	Corrected *P*[a]
Externalizing problems	4977	59.8	11.6	155	62.8	11.1	.001	3.7407	<.0001
Attention problems	4977	65.7	10.0	155	70.3	10.3	<.001	3.5208	<.0001
ADHD problems	4970	62.0	8.6	155	65.0	9.7	<.001	2.4943	.0003
Internalizing problems	4976	63.0	9.8	155	65.5	9.2	.001	2.6427	.0010
Anxious/depressed	4977	58.6	9.3	155	62.3	9.8	<.001	2.5209	.0006
Anxiety problems	4970	60.8	10.1	155	64.6	10.3	<.001	2.6581	.0010

[a] Controlled for gender, race, age at enrollment, and diagnosis in a linear regression model.

P < .001). This association remained significant when age, race, and gender were included as covariates (*P* < .001). In a follow-up analysis of the DSM-IV checklist, there were no significant differences between the adopted and nonadopted groups on overall ASD score or on individual DSM-IV items. The group association with "Impaired initiating conversation" showed *P* = .048, but this finding was interpreted as nonsignificant in the context of 12 separate items in the DSM-IV checklist. To avoid confounding, diagnosis was used as a covariate in subsequent corrected analyses.

Adopted participants scored significantly higher on the CBCL-Externalizing subscale (mean [SD] = 62.8 [11.1]) than nonadopted participants (mean [SD] = 59.8 [11.6]; *P* = .001) (Table 2). This association remained significant after controlling for demographics and diagnosis (*P* < .001). Further exploration of subvariables of externalizing behavior identified significant differences in CBCL Attention Problems (*P* < .001) and CBCL ADHD Problems (*P* < .001) between the adopted and nonadopted groups. Both variables remained significant after controlling for covariates (both *P* < .001). Diagnosis of ADHD was significantly higher in the adopted population (*P* < .001) both with and without controlling for covariates (*P* < .001), with an OR estimate of 1.9 (CI = 1.3–2.6) for the adjusted model. Adopted participants were more likely to be taking psychotropic medications (*P* < .001), with an OR estimate of 2.3 (CI = 1.6–3.3) from the adjusted model (*P* < .001). Following this trend, adoptees showed significantly higher rates of prescribed ADHD medications (*P* < .001). This association remained significant after controlling for covariates (OR = 2.0; CI = 1.4–3.0; *P* < .001). Aggression symptoms and medications for aggression were also measured, but no significant differences were observed between the adopted and nonadopted groups.

Adopted participants also scored significantly higher on the CBCL-Internalizing subscale (mean [SD] = 65.5 [9.2]) than the nonadopted group (mean [SD] = 63.0 [9.8]; *P* < .001). This finding was also true for the CBCL-Anxious/Depressed subscale (*P* < .001) and the CBCL-Anxiety Problems subscale (*P* < .001). All 3 subscales remained significant after controlling for covariates. The adopted group had significantly higher rates of anxiety medications (*P* < .001). However, after controlling for covariates, the association was no longer significant when using the *P* < .001 exploratory analysis threshold (OR = 1.8; CI =1.0–3.2; *P* = .044). Separation anxiety was also measured; however, only 4 individuals responded "yes" to having separation anxiety, resulting in insufficient power to evaluate this measure.

Significantly more sleep problems were reported in the adopted group (42.9%) than in the nonadopted group (30.7%; *P* < .001). This association remained significant in the adjusted model (OR = 1.8; CI = 1.3–2.4; *P* < .001). Adoptees also had significantly higher rates of sleep medications (22.1%) than the nonadopted group (9.9%; *P* < .001). This association remained significant after controlling for covariates (*P* < .001; OR = 2.3; CI = 1.6–3.4). There was no significant association between staying asleep/restlessness and adopted status in both the unadjusted (*P* = .053) and the adjusted (*P* = .017) analyses (OR = 1.5; CI = 1.1–2.1) when using the *P* < .001 exploratory analysis threshold. There were also no significant differences for the "problems falling asleep" variable between the adopted and nonadopted groups.

DISCUSSION

In the ATN, several demographic and behavioral patterns differentiate the adopted population from the general ASD population. Overall, the percentage of adopted children in the ATN was similar to the estimated rate of adoption in the United States.[31] As might be expected from the distribution of foreign adoptions during the ATN collection period, the adopted population included a larger percentage with Asian heritage. Notably, the adopted population contained a higher ratio of girls than is seen in the ASD population in general. Previous work suggests that girls with ASD tend to have more genetic loading than their male

counterparts, suggesting that being female is protective in some way.[32,33] However, the greater percentage of girls in the adopted population could suggest that some other risk factor or factors is more common in this population, thereby overcoming the female protective effect. Interestingly, a decreased male to female ratio in ASD has also been observed to some degree in association with prenatal valproate exposure (ie, a nongenetic risk factor for ASD).[34,35]

The adopted group was almost 2 years older at enrollment in the ATN than the nonadopted group. It is possible that some of the adopted children were adopted at a later age and therefore not able to be evaluated when younger. The age of original diagnosis was not available for most participants in the ATN database, and the age of enrollment does not always equate with the age of original diagnosis. However, if these children are indeed diagnosed at a later age, a number of factors, such as a more complex presentation or increased internalizing and externalizing symptoms, could explain this possible delay, which could result in most adopted children receiving ASD diagnoses after the age at which early, intensive behavioral interventions can be implemented.

The adopted group was diagnosed with PDD-NOS more frequently than the nonadopted group (39.3% vs 26.4%). Although the adoptees were more likely to receive a diagnosis of PDD-NOS, significant differences were not found for ADOS scores or DSM-IV symptoms. This suggests that other factors, such as a more complex presentation or less certain history, may influence clinical diagnosis in adopted children The influence of unmeasured or subjective factors in DSM-IV diagnosis is well known and was best demonstrated by Lord et al,[36] who found that expert autism centers generated very different patterns of DSM-IV diagnoses, which were not explained by ADOS scores or autism symptoms. In theory, some of these children might be similar to those with "quasi-autism" in the ERA study,[4,14] although that is difficult to assess without more data. It is also possible that clinicians are more likely to diagnose PDD-NOS in a child who has co-occurring externalizing or internalizing behaviors, resulting in other psychiatric diagnoses to which the ASD symptoms might be attributed. Previous data do suggest that co-occurring psychiatric diagnoses are more common in children with DSM-IV PDD-NOS or Asperger disorder diagnoses.[37,38] Furthermore, clinicians may attribute some symptoms to the adoption itself, particularly if there is a concern about other neurodevelopmental risk factors, such as birth family history, early neglect, abuse history, or institutional care. IQ did not differ between the groups, suggesting that the difference in diagnosis is not due to a general difference in cognitive function. Similarly, there were no significant differences in history of seizures, seizure medications, or general language delay excluding potential neurologic etiologies for differences in diagnosis.

Paralleling findings in the general population, adoptees within the ATN had significantly higher rates of externalizing behavior, including problems with attention and hyperactivity. Similarly, increased rates of internalizing behavior were also seen in adoptees, including problems with mood and anxiety symptoms. Almost half of the adopted group were taking psychotropic medications (43.6% vs 21.3%), indicating significantly higher rates in adopted children with ASD than nonadopted children with ASD. Higher rates of medication use in the adopted group might indicate increased attribution of behavioral symptoms to biology in the context of assumed genetic or environmental risk factors. Alternatively, increased rates of medication use could simply indicate that these adopted children with ASD presented with more complex or impairing symptoms across multiple domains. A number of risk factors could account for this greater psychiatric complexity, such as genetic factors, less prenatal care, in utero exposure to substances, abuse history, early deprivation or malnutrition, or adjustment to a new family or culture,[1,3–5] but the current data set does not contain details on these individual risk factors.

Previous studies found sleep problems to be a central adjustment difficulty for adoptees.[1] Within the ATN, 42.9% of caregivers of adoptees reported a sleep problem and 22.1% reported the use of sleep medications. Difficulties with sleep and daytime behavioral problems can have bidirectional influences on each other, although more work has focused on sleep problems affecting daytime behavior. Sleep problems in adoptees could stem from basic factors, such as change in routine, cultural differences, or adjustment to a new environment, or to specific factors, such as previous exposure to trauma or neglect.[36] These variables could also contribute to behavior and emotional problems such as anxiety or hyperactivity, which can cause sleep difficulties. This bidirectional relationship between internalizing and externalizing behaviors and sleep problems could also perpetuate a cycle that amplifies problems in both domains.[1,39,40]

To our knowledge, this is the largest sample of adoptees with ASD to be analyzed, but the current study faced important limitations. The largest challenge is the absence of specific data surrounding adoption, such as

birth parent history, pregnancy history, age of adoption, or history of institutionalization, any of which could be expected to affect neurodevelopmental outcomes.[1,3–5] Another limitation is that the ATN data analyzed here were collected at baseline visits, preventing longitudinal analysis of individual participants, which could clarify whether ASD and co-occurring symptoms evolve over time in this population. Furthermore, we lacked a control group of adopted children without ASD, the majority of whom we would expect to develop typically.

Overall, our results highlight the need for further research into ASD in the adopted population. From a clinical perspective, adopted children with ASD present with more complex patterns of symptoms, including more co-occurring behavioral symptoms that could drive a doubling in the use of psychotropic medications. Adopted children also had an increased rate of PDD-NOS diagnosis and were enrolled at a later age, which may reflect difficulty assessing ASD in the context of a more complex behavioral pattern. On the basis of these data, we would encourage clinicians to screen adopted children for ASD symptoms early and to consider an ASD diagnosis regardless of co-occurring behavioral or sleep symptoms in this population.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
ADOS: Autism Diagnostic Observation Schedule
ASD: autism spectrum disorder, ATN, Autism Treatment Network
CBCL: Child Behavior Checklist
CSHQ: Children's Sleep Habits Questionnaire
DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
ERA: English Romanian Adoption
OR: odds ratio
PDD-NOS: pervasive developmental disorder–not otherwise specified
CI: Confidence Interval

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