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Clinical evidence that Asperger's disorder is a mild form of autism

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Abstract

Objective: The aim of this study is to obtain clinical evidence to test the hypothesis that Asperger's disorder (AD) is a mild form of autism (AU).
Method: A 78-item Likert scale (the RAADS) was administered to 25 adults with AD and 19 with AU (ages, 18-65 years) to assess presence, type, and duration of symptoms.
Results: The following results were found: (*a*) subjects with AD and AU have similar symptoms throughout adulthood (responses to 72 of 78 questions were not significantly different); (*b*) subjects with AD had a significantly fewer total number of symptoms; (*c*) subjects with AD reported nonsignificantly fewer symptoms in the *DSM-IV-TR* domains of social interaction and repetitive patterns of behavior; and (*d*) subjects with AD had significantly fewer symptoms in the communication domain.
Conclusions: The data support the hypothesis that AD is a mild form of AU, and that they share a common etiology and developmental neuropathology. It appears warranted in future diagnostic manuals to incorporate AU and AD into 1 diagnostic category such as, "Autism Spectrum Disorder, (with modifiers, severe, moderate, mild, atypical, and Asperger's type)."

1. Introduction

Shortly after Asperger's [1] description of patients with "autistic psychopathy" was translated into English by Lorna Wing in 1981 [2], debate arose regarding their relationship to patients Kanner [3] described as having "autistic disturbances of affective contact." Some theorized that they were separate disorders, whereas others stated that Asperger's disorder (AD) was a mild form of autistic disorder (AU) [4-8].

In the early 1980s, we began to study the relationship of the 2 disorders in an attempt to clarify the confusion in the field. Freeman et al [9] described children with mild developmental delays and mild symptoms, whom we labeled as having a "forme fruste" of autism. We also reported nondiagnosed parents of autistic children who had mild symptoms themselves [10,11]. These cases suggested the need to broaden the phenotype of autism beyond those severely impaired cases initially described by Kanner. However, these studies were small and provided future research direction but not conclusive answers.

The initial debate was resolved for practical purposes in the early 1990s with the publication of *ICD-10* [12] and *DSM-IV* [13]. They established "official" clinical parameters for making the distinction between AU and AD based on the time of onset of language and certain cognitive functions. Designating differentiating criteria was done for heuristic purposes, with the expectation that ongoing research would soon provide pathognomonic markers that would determine whether they were distinct disorders or the same, differing only in degree of severity (personal communication, *DSM-IV* committee).

Recently, Baron-Cohen [14] introduced a new theory in an attempt to explain the relationship of the 2 disorders. It proposed that symptoms of AU and AD are not evidence of pathologic development but are normal traits that have become expressed to an extreme degree in certain individuals.

To date, no distinguishing markers have been identified, and the debate continues. One reason is the difficulty in applying the diagnostic criteria for AD as demonstrated in

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2 recent studies. Tyron et al [15] carefully rediagnosed 26 children who had previously been diagnosed as having AD. Surprisingly, they were not able to reconfirm the diagnosis in even one of these 26 children. Klin et al [16], in a complex and detailed study, had 2 highly experienced clinicians independently diagnose 65 subjects, 8 to 32 years old. They used 3 definitions of AD (*DSM-IV*, Speech Delay, and a "New System"), as well as *DSM-IV* definitions of AU, Pervasive Developmental Disorder Not Otherwise Specified, and Non-Pervasive Developmental Disorder. They found that only 44% of the subjects received the diagnosis of AD by all 3 of the diagnostic criteria for AD.

The present study was designed to obtain clinical data to help further our understanding of the relationship of AD with AU. We postulated that (*a*) AD is a mild form (phenotype) of AU; (*b*) both are caused by the same abnormal genetic programming of brain development; and (*c*) both express the same developmental brain neuropathology that is manifested clinically by separation (lack of normal coordination) of the 3 main developmental pathways (social interaction, communication, and repetitive behaviors) and by delays, spurts, and plateaus of brain development [17].

The literature supports a common etiology due to abnormal genetic programming: (*a*) the original suggestions of both Kanner [3] and Asperger [1] that "familial factors are involved"; (*b*) the high concordance rate in monozygotic twins [18,19] and the high sibling recurrence risk estimate [20]; (*c*) evidence of delayed maturation of brain volume [21]; and (*d*) common abnormalities in neurotransmitters (ie, serotonin and melatonin) [22,23]. In addition, an international multicenter study recently identified candidate genes that may be associated with both AD and AU [24].

For this study, 3 specific hypotheses were established for empirical testing. They stated that if AD is a mild form of AU, then (*a*) similar symptoms will be present in both disorders throughout adulthood, (*b*) subjects with AD will have fewer overall symptoms than subjects with AU, and (*c*) subjects with AD will have fewer symptoms than subjects with AU in each of the 3 *DSM-IV-TR* symptom domains [25].

To obtain data on specific symptoms to test these hypotheses, we administered an empirically based 78-item, self-rating scale (the RAADS) [26] to 25 adults with AD and 19 with AU. It uses a developmentally based Likert scale to quantify the presence, distribution, and longevity of specific symptoms.

2. Method

2.1. Subjects

Forty-four subjects were recruited from (*a*) previously diagnosed patients of the investigators and clinicians known to the authors to be experts in developmental disabilities; (*b*) national autism and AU and AD support groups; (*c*) referrals from AU and AD diagnostic clinics that were familiar with the project; and (*d*) advertisements on websites for adults with AU and AD. Subjects were enrolled in the order in which they volunteered (see Table 1 for demographics).

Table 1
Participant demographics

Participant group	Number	Male/ Female ratio	Mean age	Education high school (%)	Education college (%)	Married (%)
AD	25	2.13	38.2	28	64	17
AU	19	1.71	34.9	42	26	16

2.2. Diagnostic evaluations and subject assignments

Two diagnosticians on the research team who were blind to each other's diagnoses evaluated all subjects independently. When the blind was broken, it was found that all their diagnoses were concordant. *ICD-10* [12] and *DSM-IV-TR* [25] criteria for AD or AU were used with the time of onset of language and cognitive functioning as distinguishing criteria. Each evaluation consisted of reviewing prior medical records when available, obtaining a developmental history, and conducting an interview and a mental status examination. Medical records were available on 41 subjects. In addition, parental interviews were conducted to confirm clinical course and history. (Parents of 35 subjects were available for interviews.)

Two months after the initial interviews, all subjects were evaluated using "a gold standard" diagnostic system—the ADI/ADOS. This was done to confirm validity of clinical diagnosis, as well as concurrent validity of *DSM-IV-TR* criteria and the RAADS. All subjects scored above the cutoff level for autism/Pervasive Developmental Disorder Not Otherwise Specified.

The following were the inclusion criteria: (*a*) a prior diagnosis of AD or AU; (*b*) a current rediagnosis of AU or AD reached by agreement between the 2 diagnosticians who were blind to each other's conclusions; (*c*) confirmation of diagnosis on ADI/ADOS; (*d*) willingness to participate and to sign the informed consent document; (*e*) age 18 or older; (*f*) completed high school; (*g*) clinical evidence of a nonretarded verbal IQ; (*h*) demonstrated ability to read, understand, and appropriately answer questions on the scale; (*i*) a driver's license; and (j) good general health now and in the past.

The following were the exclusion criteria: (*a*) a history or clinical evidence of a medial condition other than AU or AD that could affect normal brain development; (*b*) the presence of any other *DSM-IV-TR* Axis I diagnosis; and (*c*) taking any psychoactive or other medications that could interfere with cognition or answering the scale in any manner.

2.3. Informed consent

The California Institutional Review Board, Inc, located in Pasadena, CA, approved the consent form and scale (IRB

Table 2
Comparison of total mean scores

Participant group	No. of subjects	Mean RAADS scores	Range	*t*	*df*	*P*
AU	19	1.98	1.4-2.51	2.09	42	.043
AD	25	1.69	0.0-2			

#06-001, January 27, 2006). After complete description of the study to participants, written informed consent was obtained.

The RAADS was used to obtain clinical data on individuals. It is a 78-item questionnaire formulated on an empirical basis to identify symptoms in the 3 main symptom domains in the *ICD-10* and the *DSM-IV-TR*. These are (*a*) qualitative impairments in social interaction; (*b*) qualitative impairments in communication; and (*c*) restricted repetitive and stereotyped patterns of behavior, interests, and sensorimotor symptoms. Each question is worded from the patient's point of view (in the first person, as the scale is of the self-rating type) and assigned to 1 of the 3 main symptom domains, relabeled for simplicity: (*a*) social interaction (31 questions), (*b*) communication (23 questions), and (*c*) restricted patterns of behavior/sensorimotor (24 questions).

The RAADS uses a 4-point developmentally based Likert scale to quantify the presence, time of onset, and duration of specific symptoms, and subsets of symptoms. The possible answers are (*a*) "True now and when I was young"; (*b*) "True only now"; (*c*) "True only when I was young" (before age 16); and (*d*) "Never true." Pilot data on the RAADS yield good internal consistencies. Factor analysis results also support the validity of the RAADS [26].

2.4. Data analysis

All identifying information was coded to preserve anonymity and was entered with responses to the questionnaire into Excel spreadsheets and then transferred to the SAS program for statistical analyses. Analyses of covariance for demographic factors were conducted; *t* tests were used to compare AU and AD group mean responses and responses to each of the 78 questions.

2.5. Administration of the scale

A member of the research team explained the scale, obtained informed consent, and remained with each subject while the questions were being answered. This was done to assure that subjects attended to the task and allowed for answering questions. All subjects completed the scale in less than 45 minutes, most in less than half an hour.

Table 3
Comparison of scores on 6 of 78 questions that were significantly different

Question number	AU mean	AD mean	*t*	*df*	*P*	Domain
26	2.21	1.44	2.09	42	.042	Language
46	1.58	0.92	2.10	42	.041	Social
68	2.16	0.92	3.57	42	.0009	Language
72	2.53	1.72	2.03	42	.049	Language
74	1.26	0.48	2.95	42	.005	Social
75	2.27	1.48	2.15	42	.007	Sensorimotor

Table 4
Comparison of scores assessing duration of symptoms

Type of answer on Likert scale	AU	AD	*t*	*df*	*P*
True now and when young	40.7	37.0	1.06	42	.30
True only now	2.89	1.56	1.49	42	.14
True only when young	21.3	16.8	1.49	42	.14
Never true	13.1	22.5	3.96	42	.03

3. Results

1. Subjects with AD had significantly less total number of symptoms than the subjects with AU. This is consistent with their having a milder clinical course (see Table 2).
2. Subjects with AD and AU share the same symptoms and experience them in a similar subjective manner throughout adulthood (see Table 3). *t* test comparisons of the 78 questions revealed that only 6 (7%) were significantly different. These 6 questions were in the symptom domains of communication (3), social interaction (2), repetitive patterns (1).
3. Subjects with AD reported nonsignificantly fewer symptoms on 3 of the scale's categories (true now and when I was young, true only now, and true only when I was young). This indicates that the symptoms of AD, although similar, are milder from childhood through adulthood. These results suggest that AD and AU cannot be distinguished solely on the basis of how long symptoms persist or when and if they abate (see Table 4).
4. Subjects with AD answered significantly more often the category, "These (symptoms) were never true." This is consistent with the hypothesis that they have a milder clinical course. In addition, it accounts for the first result reported that the total number of symptoms was significantly less in the subjects with AD (see Table 4).
5. Subjects with AD had significantly fewer symptoms in the communication domain. They also had nonsignificantly fewer symptoms in the social interaction and restricted patterns of behavior domains. These results indicate that the core symptoms in 3 main developmental domains widely overlap (see Table 5).

Table 5
Comparison of scores in 3 major symptom domains

Symptom domain	AU	AD	*t*	*df*	*P*
Social interaction (31 questions)	1.79	1.52	1.91	42	.34
Communication (23 questions)	2.07	1.76	2.37	42	.02
Restricted patterns (24 questions)	1.92	1.83	0.62	42	.54

Each of these results is consistent with the main hypothesis that AD is a mild form of AU, and that both disorders share the same etiology and developmental neuropathology.

4. Discussion

4.1. Limitations

Four methodological problems require comment and careful consideration. First, according to *ICD-10* and *DSM-IV-TR*, an accurate history of the time of onset of language and cognitive functioning is required to distinguish between AU and AD. Fortunately, only 3 (6%) of our 44 subjects lacked confirmatory information. Confirmatory information was obtained from medical records (41 subjects) and parental reports (35 parents). In the 3 cases where we could not confirm, we relied on the subjects' best recollection of what they had been told. Unfortunately, this problem will plague clinicians and researchers as long as the diagnosis requires the availability of information that may not be available.

A second methodological problem was posed because the research diagnosticians were aware that the subjects had previously been diagnosed with either AU or AD. However, they were blind to each other's diagnoses, and they had agreed on each subject's diagnosis when the blind was broken. This problem was addressed by the administration of the ADI/ADOS to confirm diagnoses.

A third limitation was the small sample size, since there were only 44 subjects. Further replication on a larger sample is being conducted.

A fourth limitation was the fact that although the RAADS measures total number of symptoms, it does not quantify duration and severity. Those are equally important diagnostic determinants. This needs to be addressed in a further study when differentiating autism from AD.

4.2. Theoretical implications

The results support the main theoretical assumption of the study, namely that AD is a mild form of AU. This does not preclude other interpretations.

Recent research suggests that the etiology of both may be found in the genes that program and coordinate brain development and probably not in the genes that code for the protein building blocks of the brain itself. This is compatible with the data. A new field of RNA analysis is emerging [27]. It is to be hoped that it will provide tools that will allow us to pinpoint the gene or genes that contain the aberrant blueprints for brain development.

4.3. Clinical implications

As Klin et al [16] and Tyron et al [15] demonstrated in the studies previously cited, much confusion exists in the minds of our patients, their families, and professionals concerning the relationship between AD and AU. Asperger disorder has become the "preferred diagnosis," and it is often used inappropriately. This leads to the unfortunate circumstance that many patients diagnosed as having AD are unable to receive the social support and educational services they need and are entitled to receive. This is due to the fact that it took decades of advocacy work by parents and professionals to get these services "approved" for AU by insurance companies and state and federal agencies, and most are not yet approved for AD. Thus, many children and adults are left with a "better diagnosis" but no access to needed services.

To mitigate the possibility that our patients will be excluded from appropriate services, we carefully explain the background of all relevant diagnostic terms to them and their families and stress their potential impact on access to services. For pragmatic purposes, we use the diagnostic label of AU for patients who have developmental delays and spurt and other symptoms indicative of AU. This allows them to receive appropriate medical, social support, and educational services.

5. Conclusions

The data indicate that in adults (age 18 years and older), the symptoms of AU and AD overlap and cannot be separated by assessing their specific type, duration, or distribution according to the area of development affected. In addition, subjects with AD have significantly fewer symptoms. These results are consistent with the hypothesis that AD is a mild form of AU, and that they share the same etiology and underlying developmental neuropathology.

Based on these results and results of other previously cited studies, it appears reasonable to suggest that AU and AD should be included within the same diagnostic category in future editions of the *ICD* and the *DSM*. We propose: Autism Spectrum Disorder, with modifying codes for severe, moderate, mild, Asperger's, atypical, and subclinical types.

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