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Nosological and Genetic Aspects of Asperger Syndrome

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The validity of Asperger syndrome (i.e., apart from high-functioning autism) continues to be the topic of considerable debate. Consistent with Asperger's original description of the condition there appear to be some important potential differences from autism if both conditions are strictly defined. Although the importance of genetic factors in the transmission of autism is increasingly clear it also appears that genetic factors may play an even more important role in Asperger syndrome (AS). The nosological validity of this condition and its relation to the various PDD spectrum disorder remains an important topic for future research. Well-designed and carefully controlled studies are needed in which patterns of comorbidity and associated problems in family members can be carefully assessed. Such studies will contribute to our understanding of the relationship of AS and autism and may clarify important genetic mechanisms of relevance to autism.

KEY WORDS: Asperger disorder; genetics; nosology; autism.

INTRODUCTION

There is little disagreement that severe social and cognitive deficits are major components of the autistic phenotype and that less severe forms occur more frequently than expected by chance among the relatives of individuals with autism (Rutter, Bailey, Simonoff, & Pickles, 1997). More controversy surrounds genetic aspects of the conditions which have been included in the broad spectrum of disorders encompassed in the Pervasive Developmental Disorder (PDD) class in DSM-IV (American Psychiatric Association [APA], 1994) and ICD-10 (World Health Organization [WHO], 1993). Although autism has been widely recognized as the prototypic PDD the other conditions presently included in the PDD class share some important similarities to autism. For several different reasons considerable interest has focused on the condition now known as Asperger disorder or Asperger syndrome (AS).

Asperger's (1944/1991) original description of the syndrome he termed "autistic psychopathy" shared, to some extent, the clinical features presented, unbeknownst to Asperger, in Kanner's (1943) description of autism. This was particularly true relative to the marked problems in social interaction. It differed from autism in that speech was less commonly delayed and motor deficits more common. Asperger also suggested that similar, if less severe, problems in social interaction were observed frequently in family members, particularly fathers (Klin & Volkmar, 1997). Despite Asperger's original speculation about the prominence of what appeared to be genetic factors, relatively little systematic research has, to date, been conducted on this aspect of the condition.

DEVELOPMENT OF THE DIAGNOSTIC CONCEPT: ALTERNATIVE VIEWS OF THE DISORDER

Asperger (1944) described a small group of boys who exhibited marked difficulties in social interaction despite seemingly adequate cognitive and verbal skills (see Frith, 1991, for a translation of Asperger's original account). Asperger originally termed the

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condition "*Autistischen Psychopathen im Kindesalter*," or autistic personality disorders in childhood, using Bleuler's earlier (1916/1951) term "autism" to suggest the marked egocentrism of these cases. While unaware of Kanner's earlier (1943) use of the same word in the description of early infantile autism, Asperger, like Kanner, emphasized differences from schizophrenia.

In addition to the marked difficulties in social interaction Asperger also noted other features present in these cases, that is, impaired nonverbal skills, idiosyncratic communication, egocentric preoccupations and special interests, intellectualization of affect, clumsiness and poor body awareness, and conduct problems. Unlike Kanner, Asperger (1979) thought that speech and language skills early in life were apparently normal and that the condition was not usually recognized before age 3.

Asperger's work, which was published in German and during the war, received little attention for many years even though Asperger himself remained an active clinician and educator. Interestingly cases with the conditions may have been described earlier (Sussucharewa, 1926/1996) and cases with many similarities were observed in the American and English language literature in the 1950's but without any awareness of Asperger's earlier work (e.g., Robinson & Vitale, 1954). Despite a few publications (e.g., van Krevelen, 1971) Asperger syndrome was essentially unknown in the English literature until Wing's (1981) influential review.

Yet another set of issues relate to the potential overlap with alternative diagnostic concepts. Such concepts have emerged, from various disciplines, as clinician investigators have tried to account for children with unusual social skills who do not seem to exhibit typical autism. These concepts include schizoid personality (Wolff & Barlow, 1979; Wolff & Chick, 1980), Developmental Learning Disability of the Right Hemisphere or Social-Emotional Learning Disabilities (SELD; Denckla, 1983; Weintraub & Mesulam, 1983), and semantic-pragmatic disorder (Bishop, 1989, 1995; Rapin & Allen, 1983). Similarly, the profile of neuropsychological assets and deficits associated with nonverbal learning disability (Rourke, 1989) seems to frequently be associated with Asperger syndrome but not with autism (Klin, Volkmar, Sparrow, Cicchetti, & Rourke, 1995).

Although the validity of Asperger syndrome as distinct from higher functioning autism has been the topic of considerable (and continued) debate, Asperger himself (1979) suggested several important differences. For example, he believed that the condition he described was of apparently later onset than Kanner's syndrome and, in many ways, resembled an enduring personality pattern rather than a developmental disorder (see Klin, 1994). There is little disagreement that AS is on at least a descriptive continuum with autism (Rutter, 1989) and much more debate about whether it is qualitatively different from autism (Volkmar & Cohen, 1991). The lack, at least until recently, of "official" and generally accepted definitions of the disorder has been very problematic as diverse views of the condition have emerged (see Klin & Volkmar, 1997, for a review). Table I presents a comparison of various approaches to the diagnosis of this condition including Asperger's (1944) original account and later emphases and changes (Asperger, 1979; Van Krevelen, 1971), as well as those of Wing (1981), Gillberg (1989), Tantam (1988a), Szatmari *et al.* (1989), and DSM-IV/ICD-10 (APA, 1994; World Health Organization, 1993). Ghaziuddin, Tsai, and Ghaziuddin (1992) and Miller and Ozonoff (1997), among others, have noted that correspondence of these approaches to diagnosis are not straightforward. Although DSM-IV and ICD-10 are conceptually identical in the ICD-10 system some differences do exist. In both DSM-IV and ICD-10 definitions the essential points of diagnostic similarity of the conditions are the severity of the social deficits (defined the same way for both AS and autism); both systems also agree that early communicative and cognitive development should be unremarkable. This is consistent with the original reports of both Asperger (1944) and Kanner (1943). Asperger emphasized the later recognition of the condition, usually after age 3 years, while Kanner initially believed that autism was congenital in nature. Somewhat paradoxically this issue of onset is problematic for both DSM-IV and ICD-10, but particularly for DSM-IV.

For understandable reasons both DSM and ICD are "hierarchical" in nature (i.e., some disorders take precedence over others). For autism and AS the decision was made to have autism take precedence (i.e. if both diagnoses could be made the diagnosis of autism was given). Consistent with the Asperger description, in our experience it usually is true that parents indicate they did not seek out clinical evaluations for the child until the child was between 3 and 5 years of age and then did so because the child had marked problems with peers in preschool;

Table I. Comparison of Three Sets of Clinical Criteria Defining Asperger Disorder[a]

	Asperger (1944, 1979)	Wing (1981)	DSM-IV (APA, 1994)/ICD-10 (WHO, 1993)
		Clinical feature	
Social impairment	**Yes**	**Yes**	**Yes**
Poor nonverbal communication	**Yes**	**Yes**	Yes
Poor empathy	**Yes**	**Yes**	Yes
Failure to develop friendship	**Yes**	**Yes**	Yes
Language/communication			
Poor prosody and pragmatics	**Yes**	**Yes**	Not stated
Idiosyncratic language	**Yes**	**Yes**	Not stated
Impoverished imaginative play	Yes	**Yes**	Not stated
All absorbing interest	**Yes**	**Yes**	Often
Motor clumsiness	**Yes**	**Yes**	Often
		Historical information	
Onset (0-3 years)			
Speech delays/deviance	**No**	**No**	**No**
Cognitive delays	**No**	**No**	**No**
Motor delays	Yes	Yes	May be present
		Exclusionary rules	
Exclusion of autism	Yes (1979)	No	**Yes**
Mental retardation	**No**	May be present	Not stated

[a]Symptoms defined as necessary for the presence of the condition are given in bold. Table adapted from *Asperger's Syndrome* (Klin & Volkmar, 1997).

these parents also usually do not report early concern about the child's cognitive or communicative development. However, sometimes if a very detailed and probing history is taken by a diligent clinician, parents, with the wisdom of hindsight, may report *some* problem in social interaction before the time. This raises the distinct possibility that the child may meet the onset criteria for autism, particularly in DSM-IV where this criterion is less detailed and specific than in ICD-10; if the onset criterion is met and the child presently exhibits a severe social interaction, circumscribed interest, and one of the language/communication criteria, a diagnosis of autism should technically be given. In this regard, particularly with older children and adolescents, some unusual prosody or other communicative abnormality may exist at the time of the assessment (consistent with Asperger's impression that his patients tended to become "little professors") even when early language development was normal. It is hoped that subsequent versions of DSM and ICD will address this issue.

The final set of diagnostic issues have to do with the relationship of AS with other disorders. Such association, if confirmed, have potential implications for clarifying the relationship of AS with other disorders. Various reports, mostly of single cases, have suggested a potential association of the condition with violence or psychosis. Unfortunately this literature is difficult to interpret and the results of the few, better controlled, studies are contradictory (see Klin & Volkmar, 1997).

GENETIC ASPECTS OF ASPERGER SYNDROME

The evidence for a genetic contribution to the syndrome of autism comes from several lines of evidence. Twin studies have strongly supported a role of genetic factors in the pathogenesis of autism with increased concordance in monozygotic twins (Bailey *et al.*, 1995; Folstein and Rutter, 1977; Rutter *et al.*, 1997; Steffenburg., *et al*, 1989). This is consistent with the results of family studies which have reported higher than expected rates of the condition in other family members (Bolton *et al.*, 1994; Jorde *et al.*,

1991; Piven *et al.*, 1990; Smalley, Smith, & Tanguay, 1991; Bolton, *et al.*, 1994; Szatmari *et al.*, 1993). Although autosomal recessive inheritance was suggested in one study of multiplex families (Ritvo *et al.*, 1985) problems in case ascertainment may have biased this result (Pauls, Volkmar, Klin, Schultz, & Cohen, 1997). It appears that perhaps 5% of families are multiplex (Smalley *et al.*, 1991) and it is possible that autism in those families has a different underlying etiology than that in simplex families. Jorde *et al.* (1991), Pickles *et al.* (1995), Bailey *et al.* (1995), and Bolton *et al.* (1994) suggested that there may be an epistatic, multilocus form of inheritance. The observation that monozygotic twins are not always concordant raises the possibility that nongenetic factors may be important.

Given the presumption that Asperger disorder is on some phenomenological continuum with autism, it is also important to note that autism might represent only the most severe phenotype and that the same underlying genetic liability might be expressed, albeit in milder form in AS. Recent data suggest that the cognitive and communicative deficits in autism might be part of a broader phenotype (e.g., Bailey *et al.*, 1995; Le Couteur *et al.*, 1996). This would be consistent with the fact that family studies have revealed a range of other difficulties in family members (see Bailey, Phillips, & Rutter, 1996; Piven *et al.*, 1990, 1994; Rutter *et al.*, 1997; Smalley, McCracken, & Tanguay, 1995). Although there have been family studies of individuals with autism that have examined separately the broader phenotype and psychiatric disorders in relatives of autistic individuals, no study has been of sufficient size to adequately examine both simultaneously.

Despite Asperger's initial (1944) suggestion that the condition was more common in family members, particularly fathers, research on genetic aspects of this condition is limited to a handful of case reports and some preliminary studies. This evidence falls essentially into three categories: case reports in which AS is noted in first-degree relatives of effected cases; in which the condition is associated with conditions other than autism, for which a strong genetic basis has been established; and, finally, for cases in which AS and autism are observed in family members.

Many reports of cases have noted the apparently increased frequency of social deficits and/or the syndrome itself in family members—particularly fathers (Bowman, 1988; DeLong & Dwyer, 1988; Gillberg, Gillberg, & Steffenburg, 1992; Wing, 1981). On the other hand, as noted by Wing (1981), the original impression that such conditions were confined to fathers has been modified. In one case report, (Volkmar *et al.*, 1996) a father and son with the condition were reported; both cases exhibited unusual discrepancies between verbal and performance (nonverbal) cognitive abilities favoring the former and had similar structural anomalies on magnetic resonance imaging (MRI). While the clinical literature supports the notion that the frequency of AS in fathers, in particular, is increased, the lack of controlled studies is noteworthy. At the present time this clinical impression must be regarded as a hypothesis that awaits verification.

However, a second group of case reports also supports a genetic basis for the condition relative to potential comorbid conditions observed in association with AS. This line of research is also heavily dependent on case reports rather than controlled studies. Psychiatric conditions reported in association with AS have included schizophrenia (Clarke, Littlejohns, Corbett, & Joseph, 1989; Taiminen & Helenius, 1994; Tantam, 1988a, 1988b), Tourette syndrome (Kerbeshian & Burd, 1986; Littlejohns, Clarke, & Corbett, 1990), affective disorders (Berthier, 1995; Fujikawa *et al.*, 1987), eating disorders (Gillberg & Rastam, 1992), and obsessive-compulsive disorder (Thomsen, 1994). There also has been a suggestion for an increased risk for affective disorders (Ellis, Ellis, Fraser, & Deb, 1994; Fujikawa, Kobayashi, Koga, & Murata, 1987). In a few cases AS has been reported in association with medical conditions or obvious chromosomal abnormality (Anneren, Dahl, Uddenfeldt, & Janols, 1995; Bormann-Kischkel, 1984). As with the reports of familial transmission, the body of case reports remains insufficient to prove a genetic basis.

The most convincing studies are those in which the frequency of AS, or conditions closely related to it, are observed at significantly increased frequency in family members (i.e., relative to appropriate comparison group). Such data are, to date, extremely uncommon. In a preliminary study, Pauls *et al.* (1997) provided data based on family self-report as a preliminary aspect of their larger study of AS (see Table II). While these data are also limited given the reliance of family history data as provided by parents, the results supported the role of a strong genetic component. In this preliminary report data were collected on 99 families and in 46% of families there was a positive family history of AS or something very

Table II. Preliminary Data: Yale Asperger Project[a]

	Social difficulties	Language problems	Attentional problems
Fathers	32	6	12
Mothers	14	2	4
Siblings	14	10	10
Uncles	33	8	16
Aunts	6	1	1
Cousins	13	7	17
Grandfathers	22	6	6
Grandmothers	4	0	1

[a]Data are percentage of cases.

similar to it in first-degree relatives. High rates of social disturbance were reported in both parents. As noted in Table II high rates of difficulty were observed, particularly in fathers. If a more restricted approach were used in which it appeared very probably that the parent clinically had AS or something very close to it the paternal predominance remains, albeit at a somewhat lower level (19% of fathers as opposed to 4% of mothers). While such family history data are limited, they have usually tended to underestimate true rates of illness (i.e., the results may need to be considered conservative). This study also provides some evidence for an etiological relationship between autism and AS as 3.5% of siblings also had a diagnosis of autism. Autism in siblings was twice as common in brothers and sisters and, by family report, rates of autism in first cousins were also increased. Data from the study are consistent with the hypothesis that there is a broader phenotype of social and developmental difficulties in family members, for example, 33% of fathers and 14% of mothers were reported to have significant social difficulty although only 6% of fathers and 2% of mothers were said to have language problems. Unfortunately these preliminary data are based on report of family members rather than direct assessment; at the present time we are conducting a much more intensive study in which both Asperger probands and immediate family members receive a conceptually identical battery of neuropsychological and psychiatric assessment. It is of interest that in their family study, Bolton *et al.* (1994) reported a rate of 5.8% of autism and other PDDs in the siblings and apparently at least one, if not more, of these cases may have exhibited AS. The results of this ongoing study may help to clarify the relationship of AS to other conditions.

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