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The Epidemiology of Autism Spectrum Disorders*

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Abstract

Autism spectrum disorders (ASDs) are complex, lifelong, neurode-
velopmental conditions of largely unknown cause. They are much
more common than previously believed, second in frequency only to
mental retardation among the serious developmental disorders. Al-
though a heritable component has been demonstrated in ASD etiol-
ogy, putative risk genes have yet to be identified. Environmental risk
factors may also play a role, perhaps via complex gene-environment
interactions, but no specific exposures with significant population
effects are known. A number of endogenous biomarkers associated
with autism risk have been investigated, and these may help identify
significant biologic pathways that, in turn, will aid in the discovery of
specific genes and exposures. Future epidemiologic research should
focus on expanding population-based descriptive data on ASDs, ex-
ploring candidate risk factors in large well-designed studies incorpo-
rating both genetic and environmental exposure data and address-
ing possible etiologic heterogeneity in studies that can stratify case
groups and consider alternate endophenotypes.

INTRODUCTION

ASD: autism
spectrum disorder

Autism spectrum disorders (ASDs) are a group
of neurodevelopmental disorders character-
ized by core deficits in three domains: social
interaction, communication, and repetitive or
stereotypic behavior. The degree of impair-
ment among individuals with ASD is vari-
able, but the impact on affected individuals
and their families is universally life-altering.
The condition was initially described in the
U.S. and European medical literature in the
mid-1940s; however, references to individuals
both fictional and historical who apparently
meet the ASD clinical profile go back sev-
eral centuries (178). Through the 1980s ASDs
were believed to be rare, with a prevalence
of no more than 5 per 10,000 persons (53)
and were considered more of an intriguing
clinical dilemma than a major public health
problem. Today, the prevalence of ASDs is
understood to be many times greater, with
the condition now thought to be second only

to mental retardation among the most com-
mon serious developmental disabilities in the
United States (15, 181). With this new un-
derstanding of prevalence, the societal con-
sequences of ASDs, along with the personal
consequences, are beginning to be more fully
appreciated by policymakers.

Frustratingly little is understood about the
causal mechanisms underlying this complex
disorder, and the public health sciences have
only recently begun to study these disorders
in earnest. This review provides an overview
of what is known about the epidemiology of
ASDs including case definition, natural his-
tory, public health impact, descriptive epi-
demiology, genetic epidemiology, and possi-
ble environmental risk factors and biologic
risk markers. Challenges to epidemiologic re-
search are highlighted throughout, and the
chapter concludes by discussing future direc-
tions in ASD epidemiology.

CASE DEFINITION AND NATURAL HISTORY

Diagnosis

ASDs include the three diagnoses: autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS). Here, the term autism refers to this group of diagnoses. No diagnostically informative biologic tests for autism exist. The diagnostic criteria are behavioral, including specific numbers and levels of impairment in the three core domains. Individuals with Asperger's disorder differ from those with autistic disorder because they do not experience significant language delays and consistently have average-to-above-average cognitive skills. Individuals with PDD-NOS show impairment in the core social domain, but their pattern or severity in this or in the other two core domains is insufficient to meet diagnostic criteria for autistic disorder. Recently, standardized interview (99) and direct observation (98) tools have gained acceptance in research settings, and diagnoses based on deficits in reciprocal social interaction and communication have been most reliable (99). However, refinement of tools for diagnosis in routine clinical practice and in research is ongoing. Over the past two decades the field is increasingly understanding that autism encompasses a broader range of impairment than previously thought. The spectrum nature of symptomology does not necessarily imply a single underlying etiology because the range of symptoms could be explained just as easily by multiple etiologies with overlapping impairment profiles.

Natural History

Only in the past several years have researchers been able to diagnose autism reliably as early as two to three years of age (95). Depending on the severity of the disorder, delays have been reported in initial diagnoses of 20–60 months between initial parental suspicion and diagnosis (104, 175). One study of children re-ceiving mental health services through Medicaid in Philadelphia found that, compared with white children, black children received ASD diagnoses almost three years later, on average (103). An autistic disorder diagnosis at age two tends to remain stable, but the early diagnosis of PDD-NOS may change at later ages, most typically to a diagnosis of autistic disorder (97).

ASDs present with a wide range of symptom intensity, and within each diagnostic category multiple domains of function influence the impact of the disorder. The proportion of children with ASDs reported to actually lose acquired language and social skills before the age of two (regression) ranges from 25% to 50% across studies (140). A recent multisite study reported that for most children who experienced regression, development prior to regression was clearly atypical (135). The best known predictors of functional outcome in children with autism are cognitive status, age at language acquisition, and age at diagnosis (105, 169). Prospective studies have generally found that 60%–75% of individuals with autism followed into adulthood experience poor or very poor outcomes (144). However, changes in diagnostic practice and an increase in the availability of early intervention over the past two decades may limit the generalizability of these findings to more recent birth cohorts.

Associated Conditions

Other developmental, behavioral, psychiatric, and medical conditions commonly cooccur with autism. Mental retardation (MR) has historically been an associated diagnosis in 70%–75% of children with autism. However, more recent, epidemiological surveys place the prevalence rates of MR in autism between 40% and 55% (22, 181). Behavioral difficulties may be related to core features (e.g., perseveration, obsessiveness), comorbid diagnoses or symptoms (e.g., aggression, disruption, hyperactivity, self-injury), or sensory abnormalities. Psychiatric symptoms (e.g.,

anxiety, depression) may be influenced by severity of core deficits, cognitive impairments, and/or comorbid medical disorders (54, 82).

In ∼10% of children with autism, specific genetic, neurologic, or metabolic disorders are identified as etiologic factors (47). Many other medical symptoms or disorders are commonly reported in children with autism: seizures (168), immune system dysregulation (173), gastrointestinal symptoms (81), feeding difficulties (e.g., refusal, selectivity, sensitivity to textures), and sleep disruption (130).

Interventions and Treatment Strategies

The first small study documenting positive outcomes in children with ASDs following intensive behavioral intervention was published in the late 1980s (100). Reviews of model programs and accumulated evidence since then have led to recent recommendations that young children with ASDs should receive comprehensive behaviorally based educational intervention (i.e., addressing all the core features of the disorders and associated problems) at a minimum threshold number of hours per week (118). Because the empirical support for these standards is still relatively weak and satisfactory amelioration of symptoms is extremely rare (144), a need persists for more comprehensive studies that can establish guidelines for intervention intensity and duration, age of initiation, and generalizability of strategies across diagnostic and behavioral subgroups of children.

No medications are currently available to treat the core symptoms of ASD. In general, medications are prescribed to address comorbid behaviors such as short attention span, impulsivity/hyperactivity, sleep problems, repetitive/perseverative behaviors, anxious mood, agitation, aggression, and disruptive and self-injurious behaviors (43). Surveys have estimated the prevalence of psychotropic medication use in children as high as 47% (179). Psychopharmacotherapy may enhance

behavioral intervention programs by diminishing comorbid behavioral symptoms and improving compliance or response to the treatments, but there is ongoing debate about the role of psychotropic agents (19). Use of complementary and alternative medicine approaches are also commonly reported (90), but their effectiveness remains unproven.

PUBLIC HEALTH IMPACT

Although some evidence suggests that autism may be associated with a reduced lifespan (146), most of the public health burden results from the core impairment and associated morbidities. Preliminary estimates suggest that children with autism have nine times the healthcare expenditures of other Medicaid-eligible children and three times those of children with mental retardation (102). Support services are often required throughout the lifespan, and the associated high costs are evident in the few cost studies available. For example, annual costs associated with care for a child with ASD are estimated to be between 85% and 550% higher than annual cost of care for a typically developing child (71). Average lifetime public expenditures for a person with ASD are estimated to be approximately $4.7 million. Existing national studies of children's health care have not addressed policy and service issues specific to autism (58).

The increased interest in behaviorally based educational intervention has resulted in a push for early identification of autism. However, few pediatricians routinely engage in autism screening (40), and the rates of and average age at identification vary greatly across geographic areas in the United States (104). Although early identification of autism is a public health strategy with great promise, the efficacy and effectiveness of general population-screening instruments have yet to be demonstrated. Moreover, the supply of clinics conducting comprehensive evaluation and treatment planning for children suspected of having ASDs is already outstripped by demand. Although gains have been made in

establishing early intervention programs for young children with autism, regional discrepancies in access still exist, as do large gaps in coordinated intervention strategies for older children and young adults transitioning out of the special education system.

DESCRIPTIVE EPIDEMIOLOGY

Prevalence

The most commonly reported measures of autism frequency are point prevalence or period prevalence. Incidence rates, despite their theoretical advantages for studying risk, are of more limited utility in autism epidemiology because not only is autism diagnosis distal to disease initiation but also time between initiation and diagnosis is likely influenced by a wide range of other factors potentially unrelated to risk. Cumulative incidence, however, may be informative for descriptive epidemiologic studies of birth cohorts (64). Many population-based prevalence surveys of autism have been conducted since the 1960s with a number of recent reviews summarizing these surveys and evaluating changes in reported estimates over time (48, 78, 178). Prevalence time trends for autistic disorder are available for longer time periods than for the ASDs as a group, given that PDD-NOS and Asperger's disorder diagnoses were introduced in 1987 and 1994, respectively. Autistic disorder prevalence estimates centered at ∼5 per 10,000 in the 1960s and 1970s, tended to be ∼10 per 10,000 in the 1980s, and have been highly variable since the 1990s with reported estimates as low as 5 per 10,000 and as high as 72 per 10,000 (76, 152). Several factors associated with the variation in estimates have been noted, including the size and composition of the population studied, the means of conducting initial screening for cases, and the methods and criteria by which cases are confirmed (48, 78, 178). Most recent reviews of the prevalence literature tend to conclude that prevalence of autistic disorder falls between 10 and 20 per 10,000. Re-

cent prevalence estimates for the ASDs collectively have been surprisingly consistent, in comparison with the heterogeneity of autistic disorder estimates, falling close to 60 per 10,000 (7, 13, 22, 23). However, the most recent prevalence survey available at this writing reported ASD prevalence of ASDs in a population of more than 55,000 British eight- and nine-year-olds to be more than 110 per 10,000 (8).

The epidemiologic data coupled with dramatic increases over the past 15 years in the numbers of individuals receiving services from educational and developmental disabilities service agencies under autism classifications (121, 145) have focused attention on the secular trend in autism prevalence and its underlying causes. Some of the trend in administrative data is undoubtedly artifact. For example, the U.S. special education classification of autism was introduced only in 1994, and some of the rise in reported prevalence is certainly related to expansion of the boundaries set for behaviors consistent with an autism phenotype (51, 145, 178). Nonetheless, the question of whether this historical increase can be fully accounted for by these and other changes in diagnosis and classification remains open to debate, largely because it is very difficult to develop quantifiable estimates of diagnostic effects and virtually impossible to prove or disprove temporal changes in autism population risk profiles given the condition's unknown etiology.

High-Risk Groups

Boys are affected with ASDs more frequently than are girls with an average male-to-female ratio of 4.3:1 (48). The sex ratio is modified substantially by cognitive impairment; among cases without mental retardation the sex ratio may be more than 5.5:1, whereas among those with mental retardation the sex ratio may be closer to 2:1 (48). The sex ratio is also influenced by the presence of dysmorphic features with lower male to female ratios and greater frequency of cognitive impairment reported

among cases with the presence of six or more minor dysmorphic features (108).

Little information is available about variations in prevalence by race and ethnicity, and data from U.S. studies are inconsistent. Factors that seem to influence racial and ethnic variability across studies include the case ascertainment approach, consideration of autism subtypes, and immigration status. A California study found prevalence to be higher in children with black mothers, lower in children with Mexican-born mothers, and comparable among children with white, Asian, and U.S.-born Hispanic mothers (29); whereas an Atlanta study found that black-white rates varied by autism subtype on the basis of the cognitive status of the case (181). In national surveys, frequency of parental reports of autism diagnosis is comparable in black and white children but is significantly lower in Hispanic children (142). Studies conducted outside the United States have suggested an increased risk of autism in children who had at least one immigrant parent (53, 101, 177), but this finding was not supported in the California study that found mothers immigrating from Mexico were less likely than U.S.-born Hispanic mothers to have a child with autism (29).

Positive correlations between autism prevalence and various indicators of socioeconomic status have been consistently reported (29, 65, 77, 79). Investigators have long suspected this association to be the result of ascertainment bias (177), with empirical support for this hypothesis emerging recently. However, an Atlanta study found no association between socioeconomic status and autism in children identified only in schools (which provide universal access to services) (79), and a report from Denmark, where access to health care is universal, found no association between autism and parental wealth or education (84).

Reports on the relationship between maternal age and autism prevalence have been inconsistent; some studies show increasing risk with increased maternal age (29, 55, 66) whereas others find no association (41, 75). A contributing factor to cross-study heterogeneity could be variation by autism subtype: One recent report found the maternal age association to vary by the cognitive impairment status of the case (79). Others have conjectured that maternal age serves as a proxy for another true actual risk factor, paternal age, and have shown positive associations between paternal age and autism prevalence after adjustment for maternal age (20, 87).

GENETIC EPIDEMIOLOGY

Heritability of Autism

The genetic liability to autism was reported first in 1977 on the basis of a study comparing autistic disorder concordance in 11 monozygotic (MZ) and 10 dizygotic (DZ) twin pairs (45). In the early 1990s this study's sample was doubled and standard diagnostic instruments were used, yielding 69% MZ concordance and 0% DZ concordance and providing continuing support for a large heritable component to autism risk (5). Two additional modest-sized twin studies have confirmed large differences in MZ and DZ concordance (137, 153). These existing twin studies exhibited limited statistical precision. Larger, population-based twin studies of autism are underway.

The prevalence of autistic disorder among siblings of individuals with autistic disorder ranges from 2% to 6% (6), with estimates as high as 14% for siblings of females with autistic disorder (138). Even at the lower end of this range, prevalence in siblings is many times higher than is contemporaneous population prevalence estimates, providing additional support for the heritability of autism. Family studies have also shown that ∼20% of siblings of probands with autistic disorder may have more subtle variants of the core features of ASDs such as aloofness, lack of tact, limited friendships, poor pragmatic and reciprocal language, and preference for predictable routine, which are collectively referred to as the broad autism phenotype (129). Fewer data

are available on the recurrence rates of specific ASD diagnoses other than autistic disorder and on recurrence of any type of ASD when the index proband has either Asperger's disorder or PDD-NOS.

Taken together, twin studies and family studies clearly establish that a genetic susceptibility to autism exists. Because MZ concordance is less than 100% and the degree of impairment and range of symptoms vary markedly among concordant pairs, environmental factors are most likely etiologically significant as well (5, 89). Should gene environment interaction account for some of the genetic component of autism risk, quantitative estimates of heritability can be substantially overestimated (59).

Although the heritability of autism has been established, the model of inheritance is still not clear. Segregation analyses based on pedigrees of autism families are challenged by the higher likelihood of stoppage (having fewer children than originally planned) in families affected by autism (73). Despite early reports that autism might follow a simple autosomal recessive inheritance model (139), later studies have consistently suggested more complex inheritance. Investigators have found both additive threshold (74) and epistatic models (136) to be the best fit in different sample sets. In general, however, these complex, multigene models seem most consistent with the findings from the broad autism phenotype studies, which suggest that family members with the broad autism phenotype possess fewer predisposing genetic variants than do clinical cases.

Gene-Discovery Studies

Two principal strategies exist for identifying specific autism risk genes. The first is full genome screens that use sets of polymorphic markers distributed over all chromosomes in samples of, often multiplex, autism families. The second is analyses focused on specific candidate genes believed a priori to have functional importance in a biologic mechanism

of potential etiologic relevance to ASDs. To date, results from 10 full genome screens have been published. Findings from all but one (86) have been summarized in recent reviews (4, 80). Genome screen findings have identified numerous regions of suggestive linkage, but only a subset of these overlap across studies. The lack of consistent findings may be attributable to variability in optimal criteria to define "significant" results, the presence of etiologic heterogeneity, and/or complexity of the underlying genetic mechanism.

The regions of interest identified in more than one genome screen are on chromosomes 1p, 2q, 5q, 7q, 15q, 16p, 17q, 19p, and Xq (80). One promising region appears to be the one located on chromosome 7q (4, 80). This region's plausibility is supported by the identification of chromosomal anomalies in this area in individual autism cases, the location of several candidate autism risk genes in the area, and the fact that the region continued to reach significance in a meta-analysis of six independent genome screens (166). However, the findings concerning 7q still vary substantively in terms of localization of the linkage peak and strength of the statistical association, so the region of interest on this chromosome remains quite broad and could contain more than one risk gene.

In the past ten years more than 100 candidate genes have been studied for association with ASDs (4). The fact that the list of specific genes considered is long is no surprise given that more than one third of all human genes are expressed in the developed or developing brain (16) and that there are few specific leads on pathobiologic pathways relevant to ASDs to guide candidate gene selection. Some of the candidate genes that have received the most attention include the serotonin transporter (SLC6A4 or 5-HTT) gene on chromosome 17q, the reelin (RELN) gene and the engrailed gene (EN2) on 7q, and the neuroligin genes (NLGN2 and NLGN4) on Xp and Xq, respectively (12, 131, 148, 182). However, no one has consistently replicated the positive findings for these, or any other,

candidate autism genes. Candidate gene studies must surmount the same major hurdles faced by linkage studies—the potentially complex underlying genetic mechanism and possible etiologic heterogeneity. In addition, the lack of reproducibility of candidate gene studies is potentially a product, in part, of publication bias in initial positive reports and limited statistical power in follow-up investigations.

Genetic epidemiologists have adopted many strategies in an attempt to move the field forward. The first is sample stratification by potential markers of etiologic heterogeneity. This approach involves separating family samples into groups on the basis of case and/or family member phenotypic characteristics and determining whether linkage or association is stronger in one group versus another group. This approach has shown some promise; for example, stratification by presence of language delay increased linkage signals at chromosome 2q (151). Yet, initial reports suggest that heterogeneity of study findings generally seen in candidate gene studies is persisting across the phenotypic subgroups investigated thus far. For example, Bradford et al. (18) reported a strengthening of linkage signal at 7q and 13q in the subsets of families with a history of language delay, but Spence et al. (151) were unable to replicate this finding. Similarly, whereas Molloy et al. (113) found linkage at chromosomes 21q and 7q in a subset with autism and developmental regression, Parr et al. (126) found little evidence for linkage at these sites in their autism family subset with language regression. Other behavioral characteristics that have been used to stratify samples include insistence on sameness, obsessive-compulsive behavior, and the presence of savant skills.

POTENTIAL RISK FACTORS AND RISK MARKERS

Infection and Immune Dysfunction

Converging evidence points toward an immunologic component in an unknown pro-

portion of children with autism. The pathway linking the immune system and autism is still unclear because of limitations in available data and uncertainty about the nature and timing of the neurodevelopmental process that leads to autism. Cerebral spinal fluid and peripheral blood from older children with autism often show atypical levels of autoantibodies to neural antigens, immunoglobulins, inflammatory cytokines, and other markers that may signal dysregulation and/or dysmaturation of both adaptive and innate immune systems (31, 115, 183). Postmortem central nervous sytstem tissue from individuals with autism shows evidence of innate immune system abnormalities, particularly in the cerebellum, which are thought to represent a chronic inflammatory process (171).

Less compelling evidence exists for an initiating role for infection and immune factors during the critical period of early neurodevelopment. Prenatal exposure to viral agents (e.g., cytomegalovirus, rubella) has been linked to autism, but early viral exposure is unlikely to account for many cases (91). Rodent models demonstrate that the maternal immune response to infectious exposure during critical prenatal periods can cause autistic-like behavioral changes in pups, but the applicability to human populations is uncertain (147). Early reports of a high frequency of autoimmune disorders among mothers and other relatives from self-selected subjects were not replicated in a recent population-based study of maternal autoimmune diagnoses recorded in the four-year period surrounding pregnancy (30), although familial autoimmune thyroid disease has been associated with regressive autism in another study (114). A modest association with maternal asthma and allergy diagnoses recorded during the second trimester was observed in one study (30). Limited evidence from candidate gene studies has implicated genes that regulate immune response as autism susceptibility loci (172). Early childhood exposures to antibiotic treatments and measles, mumps, and rubella (MMR) vaccination have been

hypothesized to contribute to risk of autism (42, 69). Empirical support for the antibiotic hypothesis has yet to emerge, and evidence from studies on autism and MMR does not support an association (49, 69).

These findings do not yet permit clarification of whether immune dysfunction during early neurodevelopment leads directly to central nervous system abnormalities, if an inherent central nervous system abnormality triggers an abnormal immune response or if the central nervous system and immune changes occur in parallel.

Neurotransmitters, Peptides, and Growth Factors

Neurotransmitters, neuropeptides, and neurotrophins are families of protein signaling molecules that orchestrate neurodevelopment and neural function through complex, reciprocal communication networks that include the immune and endocrine systems. Certain of these factors have been evaluated as potential contributors to the etiology of autism. As a test of the hypothesis that autism is a result of dysregulation of the normal developmental program in the brain, an initial study sought to evaluate levels of selected neuropeptides and neurotrophins in archived newborn specimens (119). Of eight analytes reported, significant case-control differences were observed for two neuropeptides (CGRP and VIP) and two neurotrophins (BDNF and NT4/5), with similar results for children with autism and children with MR compared with controls. Subsequent immunoassays employing different laboratory platforms have failed, thus far, to replicate these initial findings (120). Some limited evidence in children with autism suggests abnormal levels of BDNF (brain-derived neurotrophic factor) in peripheral blood, but the pathogenic significance of this finding is uncertain (26).

Serotonin, a neurotransmitter, has consistently been found at higher concentrations in peripheral blood of subjects with autism. Selective serotonin reuptake inhibitors (SSRIs) can ameliorate autistic behaviors in some affected individuals, and some studies indicate that manipulation of serotonin in animal models can lead to pathological findings seen in autistic brains (174). Imaging (25) and genetic studies (37) suggest that autism may be associated with abnormal serotonin synthesis. However, studies of fetal and newborn serotonin synthesis have not been reported, and the etiologic importance of serotonin is unclear. Melatonin is made in the pineal gland from serotonin, with peak secretion at night. Some, but not all, studies have shown decreased nighttime production of melatonin in individuals with autism (164) consistent with the high rate of sleep disorders in individuals with autism (130).

Oxytocin and vasopressin are structurally related peptides that have been linked to processing of social cues, social recognition, and social bonding in mammalian species (68). Polymorphisms in oxytocin receptor genes have been associated with autism in human studies (180), and complex deficits in oxytocin processing appear to be present in some children with autism (112). No association was found in one study between autism and pregnancy induction using exogenous oxytocin (50). Secretin, a peptide active in the gut and brain, was reported anecdotally to show promise as a pharmacologic intervention for autism, but subsequent clinical trials failed to demonstrate significant behavioral improvements in treated children (158).

Endocrine Factors

The study of endocrine factors in autism stems from links with other neuropsychiatric disorders and the persistent gender imbalance yet to be explained by a genetic mechanism. Abnormal sex hormone levels in pregnancy, especially testosterone with its presumed effects on sexually dimorphic brain structure and behavior, is an area of interest. However, exposure assessment is challenging, with amniotic fluid difficult to obtain and the ultimate utility of morphologic markers of in

utero exposure, such as digit length ratios, unproven. The steroid precursors DHEA (dehydroepiandrosterone) and DHEA-S (dehydroepiandrosterone sulfate) have been investigated given their role in regulating neuronal function. One study found lower DHEA and DHEA-S levels in adults with autism than in controls (157), whereas study of pubertal and prepubertal children reported no DHEA-S differences (162).

Maternal reproductive hormone dysregulation may be one mechanism leading to obstetric suboptimalities that have received attention as potential autism risk factors (discussed further in the following section). The rising use of infertility treatments has prompted general interest in their developmental consequences. However, data on infertility history in autism are scant, and elevated rates of autism have not been observed among children born after in vitro fertilization techniques (92, 127, 155). A critical consideration for future investigations is the development of approaches to distinguish the hormonal effects of treatment from other potential treatment effects, such as twinning or premature birth, and from potential effects related to the underlying causes of infertility (including advanced maternal age).

Other hormonal factors of interest have been hypothalamic/pituitary/adrenal (HPA) axis stress hormones and thyroid hormones. Given the high rate of anxiety and heightened arousal symptoms in individuals with autism, stress hormone levels have been investigated in several small case-control studies (32, 161, 163) producing variable results. However, the prenatal maternal stress response, especially before 32 weeks gestation when the fetal limbic system is considered to be most vulnerable (14), may be of potentially greater etiologic significance. Intrauterine thyroid dysfunction has been linked to neurologic deficits and has been hypothesized to contribute to autism and other neurobehavioral disorders (141). One study reported no association between neonatal thyroxine levels and autism (150), but in-

trauterine exposure may be the more relevant measure.

Obstetric Factors

Many studies have investigated associations between autism risk and maternal obstetric characteristics, labor and delivery complications, and neonatal factors. Early studies that generated initial concern tended to be small, lacked adjustment for potential confounding factors, and often relied, in part, on parent's report of obstetric complications (38, 44, 165). Several studies involved the creation of scores summarizing various combinations of maternal and neonatal factors such as maternal age, parity, intrauterine bleeding, infection, caesarian delivery, breech presentation, Rh incompatibility, neonatal birthweight, gestational age, Apgar score, and meconium staining. Most of the studies using composite suboptimality scores reported less optimal pre, peri-, and neonatal experiences among children with autism compared with both population and sibling controls (52, 96, 154, 159), but the biological mechanism underlying such associations has not been elucidated.

Recently, larger studies have evaluated individual perinatal events. Uterine bleeding, caesarian section, low birthweight, preterm delivery, and low Apgar score are among the few factors that have been more consistently associated with autism (30, 55, 66, 84). Results for most other factors have been more equivocal (30, 66, 84, 154, 159). Methodologic issues continue to challenge the synthesis and interpretation of this body of evidence. The underlying cause of a measured obstetric factor or set of factors is rarely known, nor is the temporal relationship between the obstetric event and the actual biological onset of autism.

Xenobiotic Exposure

There have been relatively few empirical investigations of potentially neurotoxic environmental or other xenobiotic exposures and autism risk, although interest remains high

given the biologic plausibility and the possibility that gene-environment interactions may underlie some of the complexity of autism inheritance (88, 122). The following sections discuss prescription medication and metal exposure, the two areas that have received the most attention to date, as well as other environmental exposures.

Prescription medications. Three medications with known teratogenic properties have been identified as potential autism risk factors. Thalidomide, prescribed in the 1950s and 1960s as a sleeping aid and to treat anxiety and morning sickness, was first linked to autism after a reexamination of 100 Swedish patients exposed to thalidomide during the first trimester of pregnancy. Four subjects met criteria for autistic disorder, suggesting a much higher prevalence of autism in this small thalidomide-exposed population. All four cases were exposed to thalidomide around 20 to 24 days after conception, offering evidence that disruption of neural tube closure may be related to autism early in pregnancy (156). Valproic acid, an antiepileptic drug also used as a mood stabilizer in bipolar disorder and schizophrenia, have been linked with autism on the basis of two small clinical series in which individuals exposed in utero showed high frequencies of autistic features (116, 132). Various animal studies have modeled potential biologic mechanisms behind these associations (67, 111, 143). Finally, survivors of labor-induced abortion using misoprostol have a higher occurrence of certain congenital anomalies, including Mobius syndrome (33). Patients with Mobius syndrome have higher-than-expected rates of autism (72), and in one recent report three out of five children with Mobius syndrome and autism had a history of in utero exposure to misoprostol (10). Although the population attributable risk associated with these relatively rare in utero drug exposures is likely quite small, these reports establish the plausibility of xenobiotic risk factors in autism etiology

and may prove useful as models for pathogenic pathways to autism.

Metals. Several metals have been associated with adverse neurodevelopmental outcomes in children and are also considered potential endocrine disruptors (EDs) (107). Although lead is a known neurotoxin and studies have found adverse effects of prenatal exposure on growth and development, surprisingly little research has been done with respect to autism (107). Mercury also has known adverse neurotoxic effects and has become ubiquitous in the global environment (1). Mercury occurs in several forms: the naturally occurring elemental (as found in outdoor air and dental amalgams), inorganic, and organic, which accumulates in the food chain as methyl mercury (primarily in fish). Several incidents of widespread methyl mercury poisoning resulted in serious neurodevelopmental impairments after prenatal exposure (9, 167), whereas longitudinal studies of less-exposed fish-eating populations have not produced consistent results with respect to cognitive deficits in children (34, 57). Ethyl mercury has been used in medical products, most notably as a preservative (thimerosal) in multi-dose vials of vaccines. Thimerosal contributes to total mercury levels in the blood, but there is little direct evidence of health effects in humans, and expert reviews have found that available evidence does not support a causal association between thimerosal-containing vaccines and autism (69, 125). Studies of mercury concentrations in hair of autistic children have yielded inconsistent results (63, 70).

Data on the developmental effects of elemental mercury are very limited. In animal studies, prenatal or early postnatal exposure resulted in subtle behavioral changes, hyperactivity, and alterations in spontaneous and learned behaviors (1). An ecologic study of industrial emissions reported a slight association of higher mercury levels with numbers of autistic children in special education, but it did not examine other, or earlier, exposures

(124). A recent study of hazardous air pollutants found a moderate association of autism with estimated airborne metal levels at birth, most notably mercury, cadmium, and nickel (176).

Other environmental exposures. Occupational exposure to solvents at chronic, high levels leads to neurotoxicity. Maternal exposure has been associated with various adverse pregnancy outcomes, including neural tube defects, as well as lower scores among offspring on subtests of intellectual, language, motor, and neurobehavioral functioning (85, 106). The study of hazardous air pollutants noted previously (176) found a moderate association with autism and estimated airborne levels of chlorinated solvents at birth. Higher estimates of diesel particulate matter concentrations during the prenatal period were also moderately associated with autism in that study, but they were also correlated with metal concentrations (176). Animal studies of diesel exhaust suggest permanent alterations in both learning ability and activity and potential endocrine disrupting effects (170). Increased indices of inflammation were seen in brains of mice exposed to airborne particulate matter (21). The relevance of these animal studies to autism is not known, but they suggest potential mechanisms and avenues for further research.

Polychlorinated bi-phenyls (PCBs) are complex mixtures of persistent contaminants stored in lipid, which have demonstrated neurotoxic and endocrine-disrupting effects in animal studies. Longitudinal studies of prenatally exposed children have found an increase in abnormal reflexes, decrease in motor skills, and cognitive deficits (133), but studies to identify autistic behaviors are lacking. Structurally similar to PCBs and found in increasing concentrations in people and the environment, brominated fire retardants (BFRs) such as polybrominated diethyl ether (PBDE) are of concern because it causes a disruption of thyroid hormone function (39). Animal studies of PBDE have indicated effects of developmental exposure on sex steroids, sexually dimorphic behavior, and neurobehavior (93).

Alcohol, Smoking and Illicit Drug Exposure

Alcohol could play a role in autism risk both directly, as a teratogen, and indirectly, via a linked genetic predisposition to both autism and alcoholism. Case reports have been published on a total of nine children affected by both fetal alcohol syndrome (FAS) and autism, or related conditions on either spectrum (2, 60, 117). However, no epidemiologic data on associations between prenatal alcohol exposure and autism risk have emerged yet, and the case report data are insufficient to conclude a link between FAS and autism (46). A number of family history studies reported higher frequency of alcoholism among family members of children with autism than among the family members of controls (109, 128, 149), but other studies found no differences (17, 84).

Smoking, illicit drug use, and other lifestyle exposures often accompany consumption of alcohol. Very few analyses have been performed of smoking in pregnancy and autism, and among completed studies, no consistent pattern has emerged (66, 75, 84). One study of a cohort of infants with prenatal cocaine exposure reported that 11% of children met diagnostic criteria for autism (36). Prenatal cocaine exposure could lead to hyperserotonemia in exposed fetuses (174), a mechanism of potential interest in autism etiology, but interpretation is complicated because of the high maternal coconsumption of other substances, including alcohol and tobacco, that may have exerted independent effects on outcome. For example, tobacco smoke exposure in pregnancy is recognized for its adverse effects on pregnancy outcome and fetal growth and development (28).

FUTURE DIRECTIONS

Although considerable advances in the epidemiologic research on autism have been

made over the past decade, gaps in knowledge remain and methodologic challenges persist. As long as autism remains a behaviorally defined condition, adequately addressing case definition issues will be central to moving forward both descriptive and analytic epidemiology. Interest concerning the meaning of secular trends in autism has been intense, but a lack of confidence in the extent to which past estimates represent true baseline levels of autism as it is now conceptualized fundamentally limit the interpretation of existing secular trend data. To overcome these limitations, prevalence surveys repeated over time in the same population need to use consistent methodology and make extra efforts to hold constant case definition criteria. A record-based autism surveillance system recently implemented in the United States (134), although likely to maintain a consistent methodology over time, still needs to pay special attention to drift in the extent of and manner in which information enters the service delivery evaluation records that provide the source data for this program.

Descriptive epidemiology should also extend beyond counting and characterization of clinically diagnosed cases to find ways to ensure that undiagnosed individuals with significant autism symptoms are also ascertained to assure accurate prevalence estimation and reduce the opportunity for selection bias to influence risk factor studies. The development of valid and reliable approaches for identifying affected persons in diverse cultures with differing public health infrastructures, however, is a challenge. Investigators need to collect additional data on the distribution of sociodemographic characteristics and traditional pre- and perinatal risk factors in samples representative of different populations. Epidemiologic inquiry in diverse populations may reveal informative variations in risk reflective of important genetic, phenotypic, or exposure variation, and assuming differences in ascertainment and diagnosis can be ruled out, may thereby provide clues to underlying etiology.

Expanded efforts are also needed to identify autism risk factors. There is certainly room for more adequately sized, well-designed studies of risk biomarkers and xenobiotic exposures. There are a number of environmental exposures, including potential endocrine disruptors such as phthalates and phenols used in plastic products, pesticides, and PBDEs, that have known neurodevelopmental effects, as well as heavy metals that may be important to consider in further risk factor investigations. Risk factor studies may be aided by case-group stratification, begun recently in candidate-gene studies because this may help overcome barriers to risk factor discovery posed by etiologic heterogeneity. Of course, behavioral domains, the most popular stratification factors so far, have not been established as important in constructing etiologically homogenous subgroups. Physical features such as head circumference, presence of gastrointestinal symptoms, or circulating serotonin levels may prove more effective for this purpose. Complex combinations of behavioral, genetic, and other biomedical characteristics may ultimately provide the most effective subtyping of autism cases.

A closely related strategy is focused analysis of phenotypic features common in autism as possible intermediate outcomes: endophenotypes. Endophenotypes are defined as heritable characteristics that might have simpler, but related, genetic roots to ASDs (56). Individual behavioral traits often considered in stratification may also be reasonable candidates for autism endophenotypes. For example, a recently developed continuous measure of social relatedness, the social reciprocity scale, may have potential as a tool characterizing an autism endophenotype (27).

Another innovative area in autism epidemiology is that of epigenetics, the study of heritable genetic factors that are not part of the DNA sequence. These likely add to the underlying complexity of disease susceptibility. One type of epigenetic factor of interest in autism is genomic imprinting, where a specific parental allele is preferentially expressed

in somatic cells of the offspring because of DNA methylation or histone modifications. Many imprinted genes are highly expressed in the brain (35), and some other known genetic disorders associated with autistic features and diagnoses, such as Prader-Willi and Angelman syndromes, result from defects in imprinting or the aberrant expression of imprinted genes (123). At this point only a few autism linkage studies have incorporated examination of parent-of-origin effects, which could elucidate epigenetic mechanisms (3, 83, 94). Epidemiologic studies looking to explore gene expression, however, face the additional challenge of inaccessibility of tissue from the organ of primary interest: the brain.

Future breakthroughs could also come from other areas. Gene-environment interaction is receiving increased attention (61, 88, 122), and large studies with the capacity to explore gene-environment hypotheses are now in the field (62). These studies have also begun to supplement binary diagnostic endpoints with data on continuous endophenotypes. Given the very early onset of abnormal development, evidence from neuroanatomic studies (11), and etiologic links to some known teratogens, there is a high likelihood that autism pathology originates in utero. Consequently, prenatal environmental exposures and gene-environment interactions involving maternal genes, such as those contributing to regulation of the intrauterine environment or detoxification of exogenous exposures during gestation, could be of prime etiologic significance. The exploration of these direct maternal genetic effects has

already begun in some candidate gene studies on the basis of case-parent trio data (24), although optimal designs to test these hypotheses involve the collection of additional genotypic data on grandparents (110). Furthermore, studies of endogenous biomarkers such as the neurotrophic, immune, and endocrine factors, in utero, at birth, and very early in life could also offer clues about dysregulated processes that might, in turn, lead to investigations of candidate genes or specific exposures known to influence these pathways. Pilot studies designed to measure exposures and biomarkers in pregnant women who already have one child with autism and prospectively follow the at-risk newborn are already under development (160). However, biomarker investigations in these studies, as with gene-expression analyses, must make use of samples collected from accessible tissue compartments.

Epidemiologic knowledge of autism should expand markedly over the next decade as more representative descriptive data accumulate and comprehensive and innovative risk factor investigations begin to yield results. Our evolved understanding of autism—once thought to be a rare condition of psychogenic origin—as a disorder with a range of phenotypes, complex genetic susceptibility, and multiple potential etiologies has influenced the design of current epidemiologic research. Although this reality is more challenging, it provides the proper context for epidemiology and other sciences to work toward much needed advances.

SUMMARY POINTS

1. Autism spectrum disorders (ASDs) are neurodevelopmental conditions with complex phenotypes and, most likely, several underlying etiologies.

2. The prevalence of ASDs in developed countries is now considered to be at least 60 per 10,000.

3. ASDs occur more commonly in boys, although the gender ratio depends on cognitive status and presence of minor dysmorphology.

4. More children are being diagnosed with ASDs today than in the past. Some of the prevalence increase is undoubtedly attributable to changing diagnostic tendency; however, there are insufficient data to determine whether this can explain the entire increasing trend.

5. ASDs are heritable, but the model of inheritance is very complex, probably involving multiple susceptibility genes. One of these yet-to-be-identified genes can probably be found on chromosome 7q. Other susceptibility genes may interact with environmental exposures or be subject to epigenetic influence.

6. A link between environmental exposures and ASDs is plausible, but little evidence exists supporting associations between specific environmental exposures and autism. Furthermore, it is not yet clear whether any specific exposures will have substantive population impact. Knowledge gained from studies of signaling proteins and endocrine factors may inform future risk factor investigations.

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