Epidemiology of Autism Spectrum Disorders

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Since Kanner’s original description of autism almost 70 years ago, the medical and sociocultural construct of autism has changed greatly and continues to remain in flux. The definition of autism, initially described as “autistic disturbances of affective contact,” has undergone a variety of changes and currently refers to a heterogeneous group of disorders. Autism spectrum disorder (ASD) is the broad term encompassing autistic disorder (AD), Asperger disorder/syndrome (AS), and pervasive developmental disorder, not otherwise specified. These disorders all share common features of impaired social relationships, impaired communication and language, and stereotypic motor mannerisms or a narrow range of interests. This article reviews the epidemiology of ASD.

The authors performed a comprehensive search of PubMed using the term autism combined with the following terms: incidence, prevalence, risk factors, associations, life span, mortality, or morbidity. The authors reviewed articles that were published within the last 5 years and printed in English. They also performed a manual search for and reviewed related articles that were referenced in the original articles. After study of these articles, the authors performed additional searches to examine specific topics not included in the initial set, such as autism, genes. They excluded case studies and case reports.

INCIDENCE

In a retrospective review of health and education records in 2006 from participating sites in the Autism and Developmental Disabilities Monitoring (ADDM) network,
the incidence of ASD is 1 child in every 110 children.² This finding is similar to the estimates that 1 in 91 children aged 3 to 17 years in the United States will be diagnosed with ASD based on data from the 2007 National Survey of Children’s Health.³ These numbers are similar to regional data whereby, in a study of birth cohorts in Massachusetts, the incidence of ASD in 2005 was 1 per 108 in children less than 3 years of age. This finding is a 66% increase in the incidence of ASD from 4 years previously, when the incidence was reported, by the same researchers using the same methodology, to be 1 in 179 children.⁴

PREVALENCE OF AUTISM IN THE UNITED STATES

Epidemiologic data gathered over the last 40 years report that the conservative estimate of ASD prevalence is 27.5 per 10,000 individuals; however, the prevalence estimate based on newer surveys is 60.0 per 10,000 individuals.⁵ A review of 23 published articles reporting the prevalence of ASD found that the pooled estimate was 20.0 per 10,000 individuals, although there was a large variation among the analyzed studies as reflected by the 95% confidence interval of 4.9 to 82.1.⁵ However, the prevalence of ASD in the United States from data gathered in the last 5 years (2006–2011) is 2 to 4 times greater than those estimates: 45 to 110 individuals with ASD per 10,000.²³⁷⁸ Even data gathered from surveys published in 2000 range from 57.9 to 67.5 per 10,000 individuals, which is almost twice the conservative estimate.⁹–¹¹ Among data collected from 11 US states in 2006, the prevalence of ASD within the states varied dramatically, with Florida having the lowest prevalence (42 per 10,000 individuals) and Missouri and Arizona having the highest prevalence (121 per 10,000 individuals).²

PREVALENCE OF AUTISM GLOBALLY

The prevalence of typical autism across the world is generally reported to be 10 per 10,000.⁵ When analyzing the prevalence of typical autism, the pooled prevalence of published reports from 37 studies was 7.1 per 10,000; however, again, there were large variations with a wide 95% confidence interval of 1.6 to 30.6.⁶ Another systematic review of 32 surveys that were published from 1966 to 2001 reporting the prevalence of typical autism found that the range of prevalence estimates of AD to be from 0.7 to 72.6 per 10,000 individuals, with a median prevalence, from studies published between 1992 to 2001, to be 12.7 per 10,000.⁵ Interestingly, the researchers noted that all the surveys with reported prevalence rates of AD of 7.0 per 10,000 or greater were published after 1987, prompting them to recalculate the prevalence estimates using only the surveys published after 1987. From these 19 surveys, the range of AD was 2.5 to 30.8 per 10,000 individuals, with an average prevalence of 11.1 per 10,000 individuals.⁵ Demonstrating a similar increase, the range of prevalence of AD in studies published after 2000 is 16.8 to 40.5 per 10,000 individuals.⁹–¹¹ A study analyzing data over an 11-year time period, from 1997 to 2008, reported the prevalence of autism in children aged 3 to 17 years to be 47 per 10,000.¹²

PREVALENCE OF AUTISM IN ASIA

The prevalence of ASD is similar in Asia. A Taiwanese 2005 national database review revealed a cumulative prevalence of ASD to be 28.72 per 10,000 individuals.¹³ This finding is a dramatic increase from the Taiwanese prevalence of 1.71 per 10,000 individuals that was reported in 1996.¹³ In Japan, the prevalence of ASD is reported to be 27.2 per 10,000 individuals.¹⁴ In Chinese children younger than 15 years of
age, the prevalence of ASD as estimated from a government registry from 1986 to 2005 is 16.1 per 10,000.\textsuperscript{15} In contrast with prevalence estimates that are similar between Asia and the United States, a South Korean study estimated the prevalence of ASD to be 1.89% of the general population of 7- to 12-year-old children. This estimation, greater than estimates elsewhere in Asia and in the United States, may be an overestimation, however, based on a low participation rate of 63%.\textsuperscript{16} In China, the prevalence of AD in children aged 2 to 6 years was 11 per 10,000.\textsuperscript{17}

PREVALENCE OF AUTISM IN EUROPE

The prevalence of ASD in Europe tends to be similar to the reported prevalence estimates in the United States and in Asia. A stratified, multiphase, random sample survey of adults living in England determined a prevalence of ASD of 98 per 10,000 individuals.\textsuperscript{18} A diagnosis survey distributed to children aged 5 to 9 years who were on the Special Educational Needs register in the United Kingdom determined the prevalence of ASD to be 94 per 10,000 and the prevalence of autism to be 11 per 10,000.\textsuperscript{19} These two studies reported a higher prevalence of ASD than other reported estimations, however. In a large population sample of children in England, the prevalence of ASD was reported to be 61.9 per 10,000. Of this group, the estimated prevalence of AD was 21.6, the estimated prevalence of atypical autism was 10.8, the estimated prevalence of AS was 16.6, and the estimated prevalence of an unspecified ASD was 13.0.\textsuperscript{20} If education records were excluded from this analysis and the data were based solely on medical records, the prevalence would have decreased by approximately 10 individuals per 10,000.\textsuperscript{21} A screening survey in the United Kingdom followed by a multidisciplinary assessment to standardize the diagnosis reported a prevalence of all pervasive developmental disorders to be 58.7 per 10,000 and a prevalence for AD to be 22.0 per 10,000 individuals.\textsuperscript{9} Another study based on the screening of more than 55,000 children aged 9 to 10 years in the United Kingdom reported that the prevalence of ASD was 77.2 per 10,000 and the prevalence of autism was 38.9 per 10,000.\textsuperscript{22} These estimations are significantly greater than the estimations outside of the United Kingdom. A report from the Danish Psychiatric Central Register estimated that the prevalence of childhood autism is 11.8 per 10,000 children less than 10 years of age and the estimated prevalence of AS is 4.7 per 10,000 children less than 10 years of age.\textsuperscript{23} In France, autism is reported to affect approximately 5 out of every 10,000 children.\textsuperscript{24}

CHANGE IN PREVALENCE SINCE 1940

Most studies conducted between 1960 and 1980 reported the prevalence of ASD to be 2 to 5 per 10,000, whereas studies published in early 2000 reported prevalences ranging from 30 to 60 per 10,000 individuals.\textsuperscript{3} This rate is still approximately half the rate that recent US studies have reported, as previously discussed. The US Department of Developmental Services reported that, between 1991 and 1997, there was a 556% increase in the prevalence of childhood autism.\textsuperscript{25} From 1997 to 2008 the rate of autism increased fourfold, from a prevalence of 0.19% in 1997 to 0.74% in 2008.\textsuperscript{12} A large retrospective review of evaluation records of American children aged 8 years in 2002 was compared with data collected by the same method 4 years later, in 2006: of the 10 states where data were collected, 9 states had an increase in the prevalence of ASD, and every state reported an increased prevalence among boys.\textsuperscript{2} Within Massachusetts, early ASD diagnosis in boys increased more than 70% from 2001 to 2005 (88 per 10,000 children for the 2001 birth cohort compared with 151 per 10,000 for the 2005 birth cohort), whereas early diagnoses in girls
increased 39% over the same time period (23 per 10,000 for the 2001 birth cohort to 32 per 10,000 for the 2005 birth cohort). From 2002 to 2006, the prevalence of identified ASD among 8-year-old children increased 57% across all sex and racial/ethnic groups. This trend of increasing prevalence has also been observed outside of the United States. A study using data from the UK General Practice Research Database showed an increase in incidence from around 0.3 per 10,000 individuals in 1989 to approximately 2.0 per 10,000 individuals by 1999. In addition, the increased risks of autism were observed in successive birth cohorts. The prevalence of ASD in Taiwan has increased from 1.71 per 10,000 individuals to 28.72 per 10,000 individuals from 1996 to 2005, based on data from the national health insurance enrollee registry. In Western Australia, the incidence of ASD increased annually with an average annual increase of 11.9% over a 17-year period, from 1985 to 2002. The overall prevalence of ASD in Western Australia among children diagnosed by 8 years of age was 8 per 10,000 births in 1983, whereas in 1999 the prevalence was 46 per 10,000 births.

One possible explanation for this change in prevalence may be an underestimation of the prevalence of autism in the past. To assess this theory, a focus group of experts in the diagnosis of AD was convened to evaluate whether the prevalence of autism may have been underestimated in a 1970s British cohort study that reported a prevalence of autism of 4.5 per 10,000, which is consistent with the prevalence reported in other studies during the same time period. This cohort reviewed the original questionnaires and found that, using contemporary diagnostic features, the prevalence of autism is 37.6 per 10,000, which is consistent with current reports. In another study, a stratified, multiphase, random sample of adults in England revealed a prevalence of ASD, recognized by survey, similar to the current reported prevalence in children, thus, adults with ASD living in the community tend to be unrecognized. This finding supports the possibility that the diagnosis of ASD is increasing in the pediatric population but not necessarily an increasing prevalence of ASD.

Another theory that has been proposed is that the increasing prevalence of autism is a result of early diagnosis, which is later revoked. However, a prospective study evaluating diagnostic stability for autism at 2 years of age and again at 9 years of age found that diagnostic stability was very high when autism was diagnosed by 2 years of age. Another study evaluating the diagnostic stability for ASD revealed that 68% of the patients diagnosed with an ASD by 2 years of age continued to meet diagnostic criteria for an ASD 2 years after the initial diagnosis. The children who no longer met diagnostic criteria for an ASD were more likely to be less than 30 months of age at the initial evaluation and, less commonly, had milder symptoms of autism or had higher cognitive scores at 2 years of age. Similar data were reported in a large survey of parents of children aged 6 to 17 years. In this study, 38.2% of all children diagnosed with autism no longer had the condition.

Another possible explanation for the increase in prevalence is the changing diagnostic criteria of autism and ASD as our knowledge of these conditions evolves. A study comparing 4 different diagnostic criteria for AS highlights the variability that can exist in the diagnosis of autism and ASD. The prevalence of AS per 1000 individuals was 2.5, 2.9, 2.7, and 1.6 based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV), International Classification of Diseases, Tenth Revision, Gillberg and Gillberg’s criteria, and Mattila and colleagues criteria, respectively. Another study, which compared the current criteria for diagnosis, the DSM-IV, with the proposed revised diagnostic criteria, DSM-5, demonstrated that the DSM-5 criteria are less sensitive than the prior criteria, especially for individuals with high-functioning autism or AS.
In addition to diagnostic criteria, the initial diagnosis may also be influenced by other factors. The type of evaluator, such as psychiatrist, psychologist, developmental pediatrician, neurologist, or school professionals, may sway the diagnosis. For example, school professionals are almost 6 times more likely to diagnose ASD.\(^3\) In a review of 78 evaluations of children diagnosed with ASD by their public school, a developmental disabilities eligibility determination, or a hospital-based early childhood mental health program, the rate of agreement by different evaluators was 45%. In addition, most community evaluators did not follow best practice guidelines or use autism diagnostic tools.\(^3\) The region of the country (Midwest, South, Northeast, and West) and urbanization of the area may also influence the diagnosis of autism: autism is significantly more likely to be diagnosed in the Northeast and in metropolitan areas.\(^3\)

Finally, the trend of increasing diagnoses of autism and ASD may reflect the success of national efforts, such as the Centers for Disease Control and Prevention’s Learn the Signs, Act Early campaign and the American Academy of Pediatrics’ Autism A.L.A.R.M. The current recommendations from the American Academy of Pediatrics is that physicians perform surveillance at each preventive care visit and screen for autism with a standardized developmental tool at specific intervals, such as the 9-, 18-, 24-, and 30-month visits.\(^3\) The American Academy of Pediatrics’ Autism Expert Panel has further recommended that physicians use an autism-specific screening tool on all children at the 18- and 24-month visit.\(^3\) There has also been increased public awareness about autism as a result of increased media attention, advocacy efforts, and celebrity publicity.

**CONDITIONS ASSOCIATED WITH AUTISM**

Although the cause of autism and ASD has not been elucidated, it is widely accepted to be a disorder of brain development. Therefore, it stands to reason that psychiatric conditions are a common comorbidity. In a large national survey, 87.3% of children aged 6 to 17 years diagnosed with ASD also had attention-deficit disorder or attention-deficit/hyperactivity disorder (ADHD), anxiety problems, behavioral or conduct problems, depression, or developmental delay. Among these conditions, the most common was attention-deficit disorder or ADHD, with an estimated prevalence of 47.2 per 100 individuals.\(^3\) There may also be a genetic component to the neuropsychiatric disorders that are frequently comorbid with autism. In a study of Swedish twins, the probability of the nonautistic monozygotic twin being diagnosed with ADHD was 44% compared with 15% for the dizygotic twin.\(^3\) A study comparing the families of an autistic child with families without an autistic child found that, in the families with autism, the frequency of social phobia was 10 times more common than among the control families. This study also found that 64% of first-degree relatives of a child with autism had a diagnosis of major depressive disorder, a statistically significant difference from the 19% with major depressive disorder among the control families.\(^3\) A Danish study reported that the risk of autism is twice as high in individuals with a maternal history of a psychiatric disorder but that there was no association between paternal history of a psychiatric disorder and the risk of autism.\(^3\) And a study evaluating obsessive-compulsive behaviors found that children with autism who displayed highly repetitive behaviors, rituals, or restricted interests were significantly more likely to have one or both parents with obsessive-compulsive traits or disorder.\(^3\)

Developmental delay and intellectual disability are also more common among children diagnosed with autism. One survey reports that 64.8% of all children with autism aged 6 to 17 years also have a developmental delay and 74.5% of children with moderate or severe autism have a developmental delay.\(^3\) Although intellectual
disability is not a defining criterion for autism, the mean distribution of IQs in individual with autism is lower than average, and approximately 40% to 60% of individuals with autism also have intellectual disability.

Genetic conditions are also associated with autism in a small percentage of individuals with ASD. Fifteen percent of individuals identified with pervasive developmental disorder had a known genetic disorder and, of these, 9% were thought to be causative of the pervasive developmental disorder, including Rett syndrome and fragile X syndrome. In a review of population-based studies of children with autism, genetic or medical conditions were found to account for less than 10% of individuals with autism. It should be noted, however, that an association with autism is not guaranteed in any of the diagnosable medical or genetic conditions that are associated with autism.

**RISK FACTORS FOR AUTISM**

There are numerous risk factors for autism that have been postulated. The following discussion is meant to discuss some of the more commonly proposed risk factors with scientific evidence to support this claim but is not inclusive of all postulated risk factors.

**Maternal and Paternal Age**

The maternal age at the time of conception and delivery may be associated with an increased risk for the child developing an ASD. Even after controlling for maternal, paternal, and infant characteristics, mothers younger than 20 years of age had the lowest odds of their child having an early ASD diagnosis when compared with mothers greater than 20 years of age. Infants born to mothers aged 20 to 24 years had lower odds of their child having an early ASD diagnosis when compared with mothers aged 25 to 29 years. In contrast, infants of mothers older than 30 years of age had increased odds of an early ASD diagnosis. In this study, paternal age was not independently associated with ASD. A Swedish study reported that a maternal age of 40 years or older was a significant risk factor for autism, with an odds ratio of 2.5. However, this study also reported that, although there was an association between advanced maternal age and a diagnosis of AS, this was not statistically significant.

Advanced paternal age may also be associated with an increased risk of autism in his offspring. After controlling for maternal age, fathers more than 50 years of age were 2.2 times more likely to have a child diagnosed with autism than a father less than 29 years of age. Another study found that children born to fathers more than 40 years of age have a 3.3 times increased odds of having ASD than children born of fathers less than 20 years of age. An Israeli study reported that children of men older than or equal to 40 years of age were 5.75 times more likely to have ASD compared with children of men less than 30 years of age, even after controlling for year of birth, socio-economic status, and maternal age. A Danish study found that the risk of autism increased with increasing paternal age: children with fathers more than 35 years of age were almost twice as likely to have a child with autism compared with fathers aged 25 to 29 years. This study, as well as 2 others, found that advanced paternal age was an independent risk factor and that advanced maternal age did not increase the risk of the child developing autism.

The combination of aging mothers and fathers may pose an additional risk to the development of autism in a child. A retrospective study of all singleton children born at Kaiser Permanente in California over a 4-year period showed that the risk of a child having ASD increased significantly with each 10-year increase in maternal age and
paternal age. Additionally, the adjusted relative risks for maternal and paternal age were elevated for children with AD and children with AS.50 A cohort study of children born in 1994 and diagnosed with ASD based on DSM-IV criteria found that both maternal and paternal age were independently associated with autism, after adjusting for birth order, maternal education, and the other parent’s age. This study also found that third- or later-born children from mothers aged 20 to 34 years and fathers less than 40 years of age were 3 times less likely to develop autism than firstborn children of 2 older parents.51

**Parental Education**

The education of parents may also play a role in the diagnosis of autism. Mothers with 4 or more years of college education had lower odds of their children having an early ASD compared with mothers who had only completed high school.4 Another survey reported that children of parents with less than 12 years of education were 68% more likely to have ASD rated as moderate and 43.5% more likely to have ASD rated as severe compared with children with ASD whose parents had more than 12 years of education.3 This increased risk may simply be an association, and more studies should be conducted to elucidate the difference.

**Child’s Sex**

The odds of a boy being diagnosed with ASD are approximately 4 times greater than girls.2–4,8 Of children in the United States diagnosed with ASD, 75% to 83% are boys.2,33,52 Internationally, the gender distribution is similar. A large-scale, retrospective study using data from the Swedish Medical Birth Registry reported that boys were 4 times more likely to be diagnosed with autism and 3.5 times more likely to be diagnosed with AS.42 Reports of boys with autism range from 79.6% in Sweden to 84.4% in Israel.42,53

**Heritability**

A genetic link to ASD seems likely, given the high recurrence rate in families. The sibling recurrence rate of pervasive developmental disorders is 7.1%,43 whereas the sibling recurrence rate of autism is reported to be between 4.5%.54 The relative risk of autism is 22 times greater in children who have a sibling diagnosed with autism and 13 times greater in children with a sibling who has been diagnosed with the broader autism diagnosis.39 In families with 2 or more children with autism, the recurrence rate is 35%.55 A study that analyzed male and female siblings separately found that the male siblings of an individual with autism have a 7% risk of having autism and an additional 7% risk for milder autistic spectrum symptoms, whereas female siblings of an individual with autism have only a 1% risk for autism.56

Twin studies further support the theory that ASD may have a genetic component. There is a higher concordance for autism among monozygotic than dizygotic twins.37 Early twin studies in the United Kingdom reported that monozygotic twins had a concordance rate greater than 60% for classic autism, and when the twin without a diagnosis of classic autism was reevaluated for broader autistic phenotypes, such as communication skills and social disorders, the concordance rate increased to 92%. In contrast, dizygotic twins had no concordance, although the concordance did increase to 10% when the twin with a diagnosis of autism was evaluated for broader autistic phenotypes. This finding supports the argument that there is a genetic predisposition to idiopathic autism.57 This data were almost duplicated in an analysis of same-sex twins less than 25 years of age in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) whereby the concordance for autism was 91% in
monozygotic twins and 0% in dizygotic twins. Similar data were reported in the largest twin study of autism to date whereby the concordance of ASD was reported to be significantly greater among monozygotic twins (88.1%) than dizygotic twins (30.5%).

This data supports a heritability component of ASD; however, only 10% of ASD can be directly attributed to an underlying medical condition, such as fragile X syndrome, and single-gene defects are rare within the broader autism phenotype. Thus, more likely, a unique set of genetic polymorphisms may determine an individual’s susceptibility to autism; however, a review of the studies detailing the mapping of these genes is beyond the scope of this article.

Paternal Factors

Beyond parental age, there are several paternal factors that may play a role in the development of ASD. For example, fathers of an autistic child respond to social cues more slowly than fathers of typically developing children. In a study of boys with AS, 15% had fathers who were also diagnosed with AS.

Low Birth Weight/Gestational Age

Another risk factor that has been repeatedly identified as a risk factor for the later diagnosis of ASD is a low birth weight or low gestational age at the time of birth. The odds of a child less than 3 years of age being diagnosed with ASD are greater for infants born preterm (birth before 37 gestational weeks) or with a low birth weight (less than 2500 g) when compared with their term or normal-weight counterparts. Other studies have shown similar associations between low birth weight and preterm delivery and the later development of autism. One reason for this may be that some of the children born preterm or with a low birth weight have other medical conditions that also predispose them to autism. Another theory that has been proposed is that children from a nonsingleton gestation have an increased risk of autism and are also more likely to have a low birth weight or low gestation age. However, data collected from the ADDM network reviewing multiple births and a diagnosis of ASD by 8 years of age from a cohort born in 1994 found no association between the autism and multiple births. In both a case-control study of Swedish children and a retrospective study of Swedish children, an association between twin gestation and autism was not identified.

Prenatal Exposures

Despite evidence linking genetics with ASD, several studies have implicated prenatal exposures as risk factors in their development. The association between congenital rubella infection and autism was initially reported as early as 1971; however, more recent data reveal that congenital rubella infection is present in only 0.75% of autistic populations, although this percentage has likely diminished with widespread usage of the measles-mumps-rubella vaccine in Western countries. Multiple studies have documented that prenatal exposure to valproic acid, ethanol, thalidomide, and misoprostol are associated with an increased incidence of autism. A 2002 study reports that maternal smoking on a daily basis in early pregnancy is associated with an increased risk of autism diagnosis of almost 1.5 times the risk of a nonsmoking mother. Not all exposures increase the risk of autism, however. One retrospective study reports that use of prenatal vitamins in the periconceptual period (the 3 months before pregnancy and during the first month of pregnancy) may be associated with a reduced risk of having a child with autism, especially in genetically susceptible mothers.
There are several proposed risk factors that have equivocal evidence. In 2 studies, black ethnicity was associated with an increased risk of autism\textsuperscript{71,72}; however, in another survey that was conducted in the United States, black children had 57\% lower odds of having ASD when compared with non-Hispanic white children. Multiracial children also had a decreased risk of being diagnosed with ASD: 42\% lower odds than non-Hispanic white children.\textsuperscript{3} Another proposed risk factor is season of conception. One study found that conception in the winter (December, January, February) is associated with a 6\% increased risk of autism when compared with a summertime conception\textsuperscript{73}; however, another study conducted in Sweden found no association between season of birth and the risk of developing autism.\textsuperscript{62}

**ANATOMIC TRAITS WITH AUTISM**

Beginning with Kanner’s original description of autism, which described an increased rate of macrocephaly, researchers continue to study anatomic traits that may be associated with autism. Dysmorphic features and minor physical anomalies are more common in individuals with autism than in the general population.\textsuperscript{58,74} In a study using a Waldrop scale to detect the presence or absence of 41 different minor physical anomalies in children with a mean age of 7 years, 96\% (n = 23) had significantly higher rates of minor physical anomalies.\textsuperscript{75} This study also found that 17\% were characterized as dysmorphic after photographs of children that had been diagnosed with syndromes associated with autism had been removed.\textsuperscript{75}

There are 4 body areas that children with ASD had significantly higher rates of minor physical anomalies: the head, ears, mouth, and hands. In addition, there are 3 minor physical anomalies that best differentiate individuals with ASD from the control subjects: abnormal head circumference, abnormal cephalic index, and abnormal palate.\textsuperscript{75} Of all anomalies, the most common physical anomaly is posterior rotation of the ears.\textsuperscript{75} Other physical abnormalities include hypertelorism, deep-set eyes, wide nasal bridge, macrocephaly, micrognathia, tapering fingers, clinodactyly, pes planus, and patchy skin pigmentation.\textsuperscript{68}

Despite Kanner’s original report, a more recent study reported that only 20\% of children with autism meet criteria for macrocephaly,\textsuperscript{76} and a separate prospective study reported that the mean head circumference for all infants that were later diagnosed with ASD was in the 84\%th percentile.\textsuperscript{77,78} However, most children with ASD are born with a significantly smaller head circumference and, in a study evaluating changes in head circumference over time, every subject in the ASD group experienced an increased rate of head circumference growth between 6 and 14 months of age. This increase in head circumference in the autistic subjects was related to a greater cerebral cortex volume at 2 to 5 years of age as demonstrated by magnetic resonance imaging.\textsuperscript{77,78} Additionally, a larger head circumference at 15 to 25 months was associated with delayed onset of language and a greater number of symptoms of social impairment based on a higher autism diagnostic interview-revised social algorithm score.\textsuperscript{78,79}

**GENETIC SYNDROMES ASSOCIATED WITH AUTISM**

Features of autism have been reported in several genetic syndromes, which are listed in Table 1.\textsuperscript{75–91}

**PROGNOSIS**

The prognosis of autism reported in the literature varies with autism severity and comorbidities. However, overall, children with autism are reported to have a poorer
health status.\textsuperscript{94} In very young children with autism, there is a strong association between autism severity and impaired cognitive function. Specifically, children with an IQ less than 70 have more social, play, and stereotyped behavior deficits than children with a borderline or normal IQ. In contrast, there is no significant difference in autism severity in children who have autism with borderline or normal cognitive function.\textsuperscript{95} However, intensive intervention can improve the social-communicative behaviors of children with autism.\textsuperscript{95} There are limited studies evaluating the lifespan of individuals with autism; however, one Danish study reported that the average age of death was 43 years.\textsuperscript{96}

**MORBIDITIES**

There are significant morbidities associated with autism and ASD. Earlier, the prevalence of psychiatric symptoms in parents of individuals with autism was discussed; however, those with autism and ASD may also suffer from psychiatric symptoms. The mean score for the Global Assessment of Functioning (GAF) scale for a group of individuals with autism who were selected from 3 population-based studies was reported to be 21.1.\textsuperscript{97} This GAF score is classified as serious impairment or inability to function in almost all areas. Additionally, 12\% of the individuals had GAF scores between 50 and 69, which indicates moderate or mild psychiatric problems or functional impairment.\textsuperscript{97} In a survey distributed to a large sample of university students in Virginia, the students who met diagnostic criteria for high-functioning ASD self-reported more problems

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Cause (if known)</th>
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<tbody>
<tr>
<td>Rett syndrome\textsuperscript{80,81}</td>
<td>Methyl-CpG-binding protein 2 mutation</td>
</tr>
<tr>
<td>Tuberous sclerosis\textsuperscript{82–84}</td>
<td>TSC1 and TSC2 mutations</td>
</tr>
<tr>
<td>Fragile X \textsuperscript{80,82,85}</td>
<td>FMR1 mutation creating triplet repeats on X chromosome</td>
</tr>
<tr>
<td>Neurofibromatosis\textsuperscript{82}</td>
<td></td>
</tr>
<tr>
<td>Congenital Rubella syndrome\textsuperscript{86}</td>
<td></td>
</tr>
<tr>
<td>Moebius syndrome\textsuperscript{82,87}</td>
<td>Underdevelopment of cranial nerves VI and VII</td>
</tr>
<tr>
<td>CHARGE syndrome\textsuperscript{75,82}</td>
<td>CHD7 mutation</td>
</tr>
<tr>
<td>Goldenhar syndrome\textsuperscript{75,82}</td>
<td></td>
</tr>
<tr>
<td>Down syndrome\textsuperscript{82,85,88}</td>
<td>Trisomy 21</td>
</tr>
<tr>
<td>Prader-Willi\textsuperscript{82,85}</td>
<td>Chromosome 15 deletion inherited paternally</td>
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<tr>
<td>Angelman syndrome\textsuperscript{82,85}</td>
<td>Chromosome 15 deletion inherited maternally</td>
</tr>
<tr>
<td>Cohen syndrome\textsuperscript{82,89}</td>
<td>Mutations in COH1</td>
</tr>
<tr>
<td>Cowden syndrome\textsuperscript{82,90}</td>
<td>PTEN tumor suppressor gene mutation</td>
</tr>
<tr>
<td>Bannayan-Riley-Ruvalcaba syndrome\textsuperscript{82,90}</td>
<td>PTEN tumor suppressor gene mutation</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome\textsuperscript{82,91}</td>
<td>Deficiency of final enzyme in pathway that synthesizes cholesterol</td>
</tr>
<tr>
<td>De Lange syndrome\textsuperscript{82}</td>
<td></td>
</tr>
<tr>
<td>DiGeorge syndrome\textsuperscript{82,92}</td>
<td>Chromosome 22q11 deletion</td>
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<tr>
<td>Wilms’ tumor, Aniridia, Genito-urinary anomalies, mental Retardation Syndrome\textsuperscript{93}</td>
<td>Chromosome 11p deletion</td>
</tr>
<tr>
<td>Smith Magenis syndrome\textsuperscript{82}</td>
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</tbody>
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with social anxiety, depression, and aggression than a matched cohort with lower autism severity scores.98

A second commonly encountered morbidity associated with autism is mental retardation. In a large retrospective study in the United States, mental retardation was present in 45% to 63% of children with autism.10 Girls with autism have been found to be more likely to have severe mental deficiency (38% of girls compared with 23% of boys); however, this does not control for syndromes associated with autism.99 A longitudinal prospective study of individuals with autism found that 30% of children diagnosed with autism tested in the mild mental retardation range (IQ 50–69) and 50% tested in the severe mental retardation range (IQ <50). In the follow-up of the same individuals 13 to 22 years later, 94% had IQs less than 70, an increase from the 80% previously.97

Neurologic dysfunction is another frequently encountered comorbidity of autism. In a recent study in the Netherlands, almost three-quarters of children with autism showed minor neurologic dysfunctions, a statistically significant number when compared with the control group, whereby only 6% had minor neurologic dysfunctions. The minor neurologic dysfunctions included dysfunctional posture and muscle tone, fine manipulative disability, mild abnormalities in coordination, and excessive associated movements.100 This finding was repeated with similar results in the United States.101 Girls with autism are more likely to have a motor deficit than boys with autism (27% vs 11%).99

Epilepsy is associated with neurologic dysfunction. A prospective study of individuals with autism reported that 38% of the studied population had epilepsy, most commonly experiencing partial seizures with or without secondarily generalized seizure activity.102 The majority had onset of epilepsy before 2 years of,102 and there is a higher risk of having epilepsy in girls with autism.103 Another study found that 14% of autistic individuals have epilepsy; however, after eliminating individuals with perinatal or medical disorder, family history of epilepsy, severe mental deficiency, or motor deficit, only 6% of individuals with autism also have epilepsy.99 This finding was supported by a meta-analysis of 24 studies that found that the prevalence of epilepsy among individuals with autism who also had intellectual disability (IQ <70) was 21.5% but only 8% in individuals with autism and no intellectual disability.103

MORTALITIES

There is excess mortality in autism, especially when comorbid with epilepsy.104 Based on data from the California Developmental Disability System from 1998 to 2002, the mortality for individuals with autism was significantly higher than that of the general population.105 A Swedish study of individuals with autism found the mortality rate to be 5.6 times higher than expected.97 A Danish study reported the risk of dying in individuals with autism was nearly twice that of the general population, and this has not changed from 1993 to 2008.96 There was an almost sixfold increase in mortality reported in a prospective study evaluating mortality in individuals with autism. Within the group of individuals with autism with early death, the rate of severe mental retardation with onset in childhood was significantly higher than in the group of living individuals with autism.97

There also seems to be a significant association between female gender and the risk of early death. A prospective study reported that 17% of the females with autism were dead in follow-up, after a period of 13 to 22 years, whereas only 4% of the males were deceased.97 Other prospective studies occurring in Sweden and the United States also reported that mortality is greater in females than males.97,106 One reason for
this may be that, because autism is more common in males as previously discussed, females with autism may be more likely to have coexisting medical disorders. However, not all sources agree. Data evaluating causes of death in autism reported no significant difference in the mortality rate between males and females with autism, although the standard mortality ratio for females is greater than that of males.\textsuperscript{105}

The increased risk of early death in individuals with autism may be associated with epilepsy.\textsuperscript{106} There is an increased risk of death when individuals with autism are comorbid for epilepsy. Almost one-third of deaths in individuals with autism are associated with epilepsy.\textsuperscript{96} The crude death rate (not adjusted for age) for individuals with autism increased 8.3 times when individuals also had a diagnosis of epilepsy.\textsuperscript{104}

SUMMARY

Autism is a life-altering diagnosis for patients, their family, and the community. As autism becomes increasingly prevalent, knowledge of ASDs is crucial for health professionals. There is ongoing debate within the literature about the cause of the increased prevalence; however, regardless of cause, physicians need to be aware of the medical implications a diagnosis of autism or ASD has. This review covers incidence, prevalence, associations, comorbidities, and mortality of ASD; however, further research is necessary to clarify controversies in many of these areas. Autism has evolved over the last 70 years since the first description by Leo Kanner and, with further research, will continue to evolve over the next 70 years.

REFERENCES


