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Advanced aging, multiple comorbidities seen in middle-aged adults with combined ASD and ID

Middle-aged adults with combined autism spectrum disorder (ASD) and intellectual disability (ID) have a high rate of comorbidities and exhibit signs of premature aging, according to a new study from France.

The study, conducted by Stéphanie Miot and colleagues, involved 63 participants with both ASD and ID. Participants were a mean age of 42.9 years. Participants with comorbid Down syndrome were excluded from the study, as this syndrome is a known cause of premature aging.

The researchers screened participants for comorbidities, ASD severity, adaptive functioning, ability to perform activities of daily living, and medication use. They also evaluated the participants' "comorbidity burden" using the Cumulative Illness Rating Scale (CIRS-G) and two subscores, the severity index (CIRS-SI) and the severe comorbidity subscore (CIRS-SC).

The researchers report, "We found a large range of comorbidities, including gastrointestinal disorders and mental and neurological diseases." Unexpectedly, they also found that 25% of the participants had chronic kidney disease.

The researchers note, "The comorbidity burden, assessed by the CIRS-G total score, of our ASD-ID population, with a mean age of 42.9 years, was comparable with that of an older population (with a mean age of 79 years) from the general hospitalized population in a geriatric department. The CIRS-SI of our sample was also higher than that of a population with a mean age of approximately 80 years, supporting the hypothesis of premature aging in ASD-ID, partially due to a high comorbidity burden." The comorbidity burden of study participants correlated with increased age, decreased ability to perform activities of daily living, and the use of multiple medications.

The researchers note that elderly people from the general population often exhibit chronic, low-level inflammation due to an imbalance between proinflammatory and anti-inflammatory cytokines—a phenomenon called *inflamm-aging*—which is associated with multimorbidity and frailty. Similarly, many studies show an association between ASD and inflammation. In this study, the researchers detected a significant association between the CIRS-G score and elevated CRP—a marker for inflammation—in their ASD group. "This inflamm-aging process," they say, "could thus partially explain such a comorbidity burden and be an indirect cause of pathological and/or premature aging in ASD."

Miot and colleagues found that the comorbidity burden of their middle-aged participants with ASD and ID was comparable to that of 79-year-olds in geriatric hospitals.

The researchers say that because their study focused on a very specific population—individuals with both ASD and ID—their results should be interpreted with caution. "The severe ID observed in our population," they say, "could be the most important cause of the observed high comorbidity burden."

They conclude, "The severity of the comorbidity burden associated with premature aging in adults with ASD and ID highlights their crucial need of personalized medical care."

Editor's note: The Autism Research Institute was instrumental in the online publication of a consensus report on aging in autism. You can view the report at www.ASDSeniorReport.com.

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"Comorbidity burden in adults with autism spectrum disorders and intellectual disabilities—a report from the EFAAR (Frailty Assessment in Aging Adults with Autism Spectrum and Intellectual Disabilities) Study," S. Miot, T. Akbaraly, C. Michelon, S. Couderc, S. Crepiat, J. Loubersac, M. C. Picot, É. Pernon, V. Gonnier, C. Jeandel, H. Blain, and A. Baghdadli, *Frontiers in Psychiatry*, September 19, 2019 (free online). Address: Stéphanie Miot, s-miot@chu-montpellier.fr.

Second study indicates link between morning sickness, ASD

New research supports an earlier study indicating that the odds of receiving an autism spectrum disorder (ASD) diagnosis are increased for children of mothers who experience hyperemesis gravidarum (HG), or extreme morning sickness.

The first study (see ARRI 33/1), by Marlena Fejzo and colleagues, involved 267 children of mothers with HG and 93 children of mothers who did not experience HG. The researchers found that by 12 years of age, children of mothers with HG had a more than three-fold increase in the odds of having a diagnosis of neurodevelopmental disorder. In this study, eight percent of the children of mothers with HG had an ASD diagnosis, compared to none in the control group.

The new study, by Darios Getahun and colleagues, focused specifically on ASD. The researchers reviewed the electronic health records of nearly 500,000 women and their children, all patients at Kaiser Permanente facilities. They found that children whose mothers had HG were 53 percent more likely to be diagnosed with ASD than children of mothers who did not have HG.

The researchers also found that HG was associated with an increased risk of autism when it was diagnosed during the first and second trimesters of pregnancy, but not when it was diagnosed only in the third trimester. HG was associated with ASD risk regardless of the severity of the HG, and medications used to treat HG did not appear to be related to ASD risk. The association between HG and ASD was stronger for girls than for boys, and stronger for white and Hispanic women than for African American women or those from the Pacific Islands.

The researchers comment, "HG diagnosis is associated with ASD risk and may be helpful in identifying at-risk children who could benefit from enhanced surveillance and earlier diagnosis and intervention."

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"Autism spectrum disorders in children exposed in utero to hyperemesis gravidarum," D. Getahun, M. J. Fassett, S. J. Jacobsen, A. H. Xiang, H. S. Takhar, D. A. Wing, and M. R. Peltier, *American Journal of Perinatology*, October 3, 2019 (epub prior to print publication). Address: Darios Getahun, Darios.T.Getahun@kp.org.

—and—

"Severe morning sickness linked with higher risk of autism," news release, Kaiser Permanente, October 3, 2019.

Post mortem study finds new evidence of immune system response targeting specific brain cells in individuals with ASD

A new study reports that the brains of individuals with autism spectrum disorder (ASD) frequently show evidence of an immune system response targeting specialized brain cells.

In the post mortem study, Marcello DiStasio and colleagues compared brains from 25 donors with ASD to brains from 30 neurotypical donors matched as closely as possible for age and medical history. In more than two-thirds of the brains of individuals with ASD, the researchers detected an excess of perivascular lymphocyte cuffs, which are accumulations of immune cells surrounding blood vessels in the brain. These cuffs are an indicator of chronic inflammation. The researchers also identified bubbles or blisters called blebs around the cuffed blood vessels, and determined that these contained debris from a type of brain cells called astrocytes.

While perivascular lymphocyte cuffing is a sign of viral infection or an autoimmune disorder, the pattern the researchers observed did not match any previously documented infection or autoimmune disorder of the brain.

Senior study author Matthew Anderson comments, "While further research is needed, determining the neuropathology of autism is an important first step to understanding both its causes and potential treatment. Investigators typically aim potential treatments at specific pathologies in brain diseases, such as the tangles and plaques that characterize Alzheimer's disease and the Lewy bodies seen in Parkinson's. Until now, we have not had a promising target like that in autism."

In separate experiments, the researchers found that the perivascular lymphocyte cuffs in the brains of individuals with ASD were composed of killer T-cells, a subset of immune cells that attack and kill damaged, infected, or cancerous cells. These killer T-cells may also target normal cells, causing autoimmune disease. The researchers speculate that either the T-cells are reacting normally to a pathogen such as a virus, or they are reacting abnormally to normal tissue.

Anderson says, "With this new research, we haven't proved causality, but this is one clue in support of the idea that autism might be an autoimmune disorder, just like multiple sclerosis is thought to be."

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"T-lymphocytes and cytotoxic astrocyte blebs correlate across autism brains," Marcello M. DiStasio, Ikue Nagakura, Monica J. Nadler, and Matthew P. Anderson, *Annals of Neurology*, October 8, 2019 (online). Address: Matthew Anderson, matthew.anderson@bidmc.harvard.edu.

—and—

"First evidence of immune response targeting brain cells in autism," Medical Xpress, October 18, 2019.

Free E-Newsletters

In collaboration with the Schafer Autism Report, the Autism Research Institute publishes an e-newsletter titled *Clinical Research in Autism*. This newsletter provides online links to up-to-date clinical research related to patient care, and is designed for pediatricians, nurses, and obstetricians (although other readers are welcome as well). You can subscribe here:

https://www.autism.org/clinical-research-e-newsletter/

The monthly ARI enewsletter includes news, webinar updates, and autism-related information and articles. You can subscribe here:

https://www.autism.org/ari-monthly-e-newsletter/

The Kids First Initiative: Giving Back to Families

The Hartwell Foundation Kids First initiative seeks to help every family who has a child with an autism spectrum disorder. The goal is to create detailed categories that accurately reflect individual behavior and personality, with the expectation of advancing personalized, targeted approaches for care and intervention that will be more successful than what is available today.

The Kids First approach is conducted using IRB-approved confidential survey methodology by prominent universities. Survey questions are simple, focused on basic behavioral and medical information, and can be completed in about 10 minutes. Results will be shared confidentially with all survey participants. The collected data will provide a unique opportunity for researchers to begin classification of ASD, and as new categories are identified, the effort will expand to more sophisticated requests for information.

We invite you to participate in the Kids First confidential survey, joining a growing network of families, clinicians, and scientists involved in this innovative research project to improve the lives of children and families affected by ASD. To learn more and begin your survey, visit kidsfirst.stanford.edu and, when asked, type ARI as your referral code.

New research implicates prenatal acetaminophen exposure in ASD and ADHD

A new study adds to evidence of an association between prenatal exposure to acetaminophen (Tylenol) and autism spectrum disorders (ASD). In addition, the study suggests that maternal use of acetaminophen during pregnancy is associated with an increased risk of attention-deficit/hyperactivity disorder (ADHD).

Yuelong Ji and colleagues analyzed umbilical cord blood samples from 996 births and measured the amount of acetaminophen and two of its byproducts in each sample. The researchers found that, by the time the children were around nine years of age, 25.8% were diagnosed with ADHD only, 6.6% with ASD only, and 4.2% with both ASD and ADHD.

The researchers divided their results into three different levels of exposure. They found that compared to children with the lowest exposure, those in the middle group were 2.14 times more likely to have ASD, and those in the highest third were 3.62 times more likely to have ASD. Compared to children with the lowest exposure, those in the middle group had 2.26 times the risk for ADHD, and those with the highest exposure had 2.86 times the risk for ADHD.

The findings follow earlier studies showing elevated rates of learning and behavior problems in children exposed prenatally to acetaminophen. In one study (see ARRI 2016, Vol. 3), Claudia Avella-Garcia and colleagues found that boys (but not girls) regularly exposed to acetaminophen in the womb had poorer scores on the Child Autism Spectrum Test (CAST) and were more likely to exhibit hyperactivity and impulsive behavior at five years of age. Earlier (see ARRI 2013, Vol. 4), Ragnhild Eek Brandlistuen and colleagues found that children exposed to prenatal acetaminophen for more than 28 days had poorer gross motor and communication skills, exhibited more behavior problems, and had higher activity levels.

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"Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood," Yuelong Ji, Romuladus E. Azuine, Yan Zhang, Wenpin Hou, Xiumei Hong, Guoying Wang, Anne Riley, Colleen Pearson, Barry Zuckerman, and Xiaobin Wang, *JAMA Psychiatry*, October 30, 2019 (epub prior to print publication). Address: Xiaobin Wang, Center on the Early Life Origins of Disease, Department of Population, Family and Reproductive Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland 21205, xwang82@jhu.edu.

—and—

"Study suggests acetaminophen in pregnancy linked to higher risk of ADHD, autism," Medical Xpress, October 30, 2019.

EDITORIAL: Stephen M. Edelson, Ph.D.

Diagnosis and screening for autism: past, present, and future

While the diagnosis of some syndromes is fairly straightforward, diagnosing autism spectrum disorders (ASD) has been and continues to be a challenge. In this editorial, I review the progress we have made in diagnosing ASD, look at the current status of screening efforts, and describe the promise and limitations of biomarkers.

The history of ASD diagnosis

In 1943, Leo Kanner wrote a detailed description of many core symptoms and behaviors of nearly a dozen individuals with autism. His description is still generally accepted within the autism community even though the diagnosis of autism has changed over the past 76 years.

The first widely accepted diagnostic criteria for autism were established by the British Working Group in 1961. This group was chaired by Dr. Mildred Creak, one of the legendary pioneers in the field. The criteria consisted of a specific list of observable symptoms and behaviors that were required in order to receive a formal diagnosis of autism.

A few years later, Dr. Bernard Rimland developed a checklist for professionals and parents that was designed specifically to diagnose Kanner's syndrome or classical autism. The first version, titled the Diagnostic Checklist for Behavior-Disturbed Children, appeared in his 1964 seminal book titled *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior*. Several years after that, Dr. Rimland published a revised version, which appeared in later editions of his book and is still distributed and scored free of charge by the Autism Research Institute.

Research on the validity of Dr. Rimland's checklist has been mixed. Unfortunately, most investigations have included children on the entire autism spectrum rather than those clinically assessed as having classical autism or Kanner syndrome.

In their first mention of autism, the American Psychiatric Association described children who exhibited "autistic, atypical and withdrawn behavior," but this was part of the diagnostic criteria for childhood schizophrenia (*Diagnostic and Statistical Manual*, *DSM-II, 1968*). It was not until 12 years later that "infantile autism" had its own category (DSM-III, 1980). Seven years after that, autism was more clearly defined in the revised edition (DSM-IIIR, 1987). Additional changes to the criteria for autism were made in DSM-IV (1994), DSM-IVR (2000), and DSM-V (2013).

Currently, several diagnostic assessment tools are based on the criteria established by the American Psychiatric Association. These include the Autism Diagnostic Interview (ADI), the Autism Diagnostic Observation Scales (ADOS), the Child Autism Spectrum Test (CAST), the Childhood Autism Rating Scale (CARS), and the Gilliam Autism Rating Scale (GARS).

It is now becoming clear that physical symptoms often associated with autism, including medical comorbidities, should be included as part of an autism diagnosis. Examples include anxiety, gastrointestinal distress, immunological and metabolic impairment, and sleep problems.

The status of screening efforts

The American Academy of Pediatrics urges that all children be evaluated for autism between the ages of 18 months and 24 months. The main goal of screening, especially during the first two years of development, is to begin early intervention services.

Screening tools have been developed to determine whether or not a child should receive extensive evaluation for autism. The most popular screening tool is the Modified Checklist for Autism in Toddlers (MCHAT), which was developed to assess children between 16 and 30 months of age.

The MCHAT, which is widely accepted as a valid screening tool for autism, was recently examined in a large-scale community-based study published in Pediatrics. The results were quite disappointing, revealing that more than 60% of children were not correctly screened for autism. As a result, numerous children may not have received life-changing intervention as early as possible.

The MCHAT, which is widely accepted as a valid screening tool for autism, was recently examined in a large-scale community-based study published in *Pediatrics*. (See article on page 6.) The results were quite disappointing, revealing that more than 60% of children were not correctly screened for autism. As a result, numerous children may not have received life-changing intervention as early as possible, and thus they may not have progressed as well as those who were properly screened.

The findings also showed that females and children of color as well as children in low-income families were often not screened properly. Not surprisingly, these findings are consistent with numerous published studies over the past five years that have documented an under-representation of autism in these three groups.

The future of biomarkers

Research on biomarkers for autism is moving forward quite rapidly, and many commercial tests will be available in the not-too-distant future. The goal of biomarker research is to identify specific biological impairments that are highly correlated with autism.

We should not assume, however, that one screening tool, diagnostic test, and/or biomarker will account for the entire autism spectrum. It may be the case that several or even many such tests will be necessary to diagnose all forms of autism.

Due to cost and/or limited availability, not all children will be able to undergo a complete battery of biomarker tests, such as analysis of blood samples and assessment of brain activity and sensory reactions. Consequently, screening tests should be designed to identify possible subtypes so that biomarkers can then be used as part of the formal diagnostic evaluation.

Due to cost and/or limited availability, not all children will be able to undergo a complete battery of biomarker tests, such as analysis of blood samples and assessment of brain activity and sensory reactions. Consequently, screening tests should be designed to identify possible subtypes so biomarkers can then be used as part of the formal diagnostic evaluation.

Since biomarkers will help us to identify specific subgroups of autism, they are likely to show that not all evidence-based treatments are optimally effective for everyone on the spectrum. Once subtypes are established, much of the research on treatments will need to be reevaluated.

Looking forward

We have come a long way since Kanner's first description of autism, but as the results of the MCHAT study show, we still have a long way to go to reach the goal of diagnosing all individuals with autism as quickly and accurately as possible.

What we now need is a coordinated effort among screening tool developers, clinicians, and researchers that will allow for a synergistic understanding of the important relationship among screening, biomarkers, and diagnosis. Furthermore, we need to close the gaps when it comes to diagnosing autism in females, children of color, and low-income children, as well as adults and seniors with ASD. The better our diagnostic and screening efforts become, the closer we will come to enabling all individuals with ASD to realize their full potential.

Research Updates

Binocular rivalry may hold clue to early diagnosis

Differences in binocular rivalry may be a marker for autism spectrum disorders (ASD), according to new research by Caroline Robertson and colleagues.

Binocular rivalry occurs when the eyes see two very different images at the same time. This causes the brain to toggle between perceiving the image seen by the left eye and the image seen by the right eye.

In earlier research, Robertson and her team showed that people with ASD make this switch between images more slowly than neurotypical individuals. They also demonstrated that this difference is due to reduced action by the inhibitory neurochemical GABA in the visual system of the brain in ASD.

In the new study, the researchers analyzed participants' responses to a test of binocular rivalry by measuring brain signals from a single electroencephalography (EEG) electrode placed over the visual region of the brain. The researchers found that based on their data, they could predict whether or not an individual had ASD with 87 percent accuracy. Moreover, participants with more severe symptoms of ASD had a slower rate of binocular rivalry than those with milder symptoms.

Robertson says, "Autism is hard to screen for in children, when the first signs are present. A trained clinician may be able to detect autism at 18 months or even younger; yet, the average age of a diagnosis of autism in the U.S. is about four years old. We need objective, non-invasive screening tools that don't depend on assessing a child's behavior. One of the big goals of the field is to develop objective neural markers of autism that can work with non-verbal individuals. This neural marker is just that."

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"Slower binocular rivalry in the autistic brain," Alina Spiegel, Jeff Mentch, Amanda Haskins, and Caroline Robertson, *Current Biology*, Vol. 29, September 9, 2019, 2948-2953. Address: caroline.e.robertson@dartmouth.edu.

—and—

"Reduced GABAergic action in the autistic brain," Caroline Robertson, Eva-Maria Ratai, and Nancy Kanwisher, *Current Biology*, Vol. 26, January 11, 2016, 80.85. Address: caroline.e.robertson@dartmouth.edu.

—and—

"New study shows how autism can be measured through a non-verbal marker," Science Daily, August 15, 2019.

ARRI Survey: Seniors with Autism Spectrum Disorder

https://www.autism.com/adult_survey

We hope the results from this survey will provide insight about the needs and challenges faced by seniors with autism (ages 50 and older) and their support providers, and better inform the autism community, government agencies, and other welfare and health-related organizations about this population's quality of life issues.

Case report: Wilson's disease misdiagnosed as Asperger syndrome

In a new case study, doctors in Japan report on a man misdiagnosed with Asperger syndrome who was later found to have Wilson's disease.

Wilson's disease is an inherited disorder in which excess amounts of copper accumulate in the body. In addition to causing liver disease, Wilson's disease can cause neurological or psychiatric symptoms including tremor, clumsiness, speech problems, cognitive problems, difficulty in swallowing, anxiety, depression, and mood swings. It often leads to the formation of a greenish-brown ring around the iris. The disease can be treated successfully with medication, especially if it is diagnosed early.

The 24-year-old patient described in the case study exhibited symptoms including behavioral problems, a lack of social awareness, and an inability to socialize, and had been diagnosed with Asperger syndrome in adolescence. He was referred to the author's hospital after he developed tremors. The authors say that based on clinical features, laboratory tests, a brain MRI, and genetic testing, they were able to confirm the diagnosis of Wilson's disease. They began treating the man with trientine hydrochloride, a drug that removes excess copper from the body, and say that "after one year of follow-up, his psychiatric symptoms have improved."

The authors conclude, "Since psychiatric symptoms may precede the neurological symptoms, the possibility of Wilson's disease should always be considered in the differential diagnosis of psychiatric disorders in young adults."

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"Wilson's disease presenting as Asperger syndrome," Kazuhiro Tomiyasu, Takeo Oshima, Masami Yoshii, Hiromi Suzuki, Joji Inamasu, and Manabu Izumi, *Rinsho Shinkeigaku*, August 30, 2019 (free online in Japanese with English abstract). Address: Kazuhiro Tomiyasu, Department of Neurology, Saiseikai Utsunomiya Hospital, Utsunomiya, Japan.

ASD. autistic traits raise risk for suicidality

A new study reports that people with either autism spectrum disorders (ASD) or autism traits have an elevated risk of mood disorders as well as suicidality.

In the study, Liliana Dell'Osso and colleagues collected data from 262 adults. Of the participants, 34 had high-functioning autism, 68 had ASD traits but did not fulfill criteria for ASD, and 160 were neurotypical controls.

The researchers assessed all participants using the Structured Clinical Interview for DSM-5 (SCID-5), which screens individuals for mental disorders. In addition, they filled out the Mood Spectrum Self Report (MOODS-SR) and the Adult Autism Subthreshold Spectrum (AdAS Spectrum).

The researchers found that individuals with ASD and autistic traits had similar scores on suicidality, and these scores were significantly higher than those for controls. They say, "This finding adds to previous literature pointing out the high rate of ASD among suicide attempters, as well as the high rates of suicidal thoughts and behaviors among patients with ASD across different age ranges." In addition, they say, the high scores on suicidality for individuals with autistic traits highlight the importance of detecting not only full-blown ASD but also subthreshold forms.

The researchers also found that individuals with ASD had significantly higher (worse) total scores on the MOOD-SR, as well as higher scores on the depressive component of this test, than individuals with autistic traits or controls. While the scores of individuals with autistic traits were lower than those of individuals with ASD, they were higher than scores for the control group.

On the SCID-5, individuals with autistic traits had a higher rate of comorbidity with other mental disorders than participants with ASD. The researchers say this may be due to the greater difficulty in diagnosing comorbid mental health conditions in people with ASD.

Overall, the researchers say, "[Our] study suggests that not only clinical ASD but also autistic traits [are] associated with a broad variety of psychopathological dimensions that include suicidal ideation and behaviors and the whole spectrum of mood manifestations, besides a number of comorbid mental disorders."

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"Mood symptoms and suicidality across the autism spectrum," L. Dell'Osso, B. Carpita, D. Muti, V. Morelli, G. Salarpi, A. Salerni, J. Scotto, G. Massimetti, C. Gesi, M. Ballerio, M.S. Signorelli, M. Luciano, P. Politi, E. Aguglia, C. Carmassi, and M. Maj, *Comprehensive Psychiatry*, Vol. 91, 2019, 34-38 (free online). Address: Barbara Carpita, barbara.capita1986@gmail.com.

Research Updates

Algorithm can predict aggressive outbursts

Researchers at Northeastern University say they have created an algorithm that can predict the violent outbursts of aggressive individuals with autism spectrum disorders (ASD) up to one minute in advance, allowing caregivers to prevent or prepare for an outburst.

Matthew Goodwin and colleagues spent 87 hours observing 20 children with ASD and aggression, using a device that helps to predict epileptic seizures (the Empatica E4 wristband) to measure the children's heart rate, sweat production, skin surface temperature, and arm movements. They then synchronized this data with clocks in biosensors the children wore. This allowed them to correlate each episode of aggression with physiological changes that occurred before, during, and after the episode.

The researchers say they were able to predict an aggressive outburst one minute in advance with 84 percent accuracy. "As our data set grows and we use more sophisticated machine learning models," Goodwin says, "I think we might get more than 60 seconds." Goodwin and his team now plan to test their approach on 240 individuals with ASD and aggressive behavior.

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"This wearable device can predict aggressive outbursts in people with autism a minute in advance," news release, Northeastern University, August 21, 2019.

Autism traits elevated in chronic depression

Autistic traits are very common in individuals with chronic depression, according to a new study by researchers in Germany and the Czech Republic.

Martina Radtke and colleagues tested 31 patients with chronic depression, 27 patients with autism spectrum disorders (ASD), and 31 neurotypical controls, using the Autism Spectrum Quotient (AQ) and the Empathy Quotient (EQ) to measure autistic traits. The researchers say, "The group of chronically depressed patients showed significantly elevated autistic traits according to both AQ and EQ measures. In addition, 48.4 percent of the patients with chronic depression showed AQ scores within the range of the broader autistic phenotype." All of the participants with ASD, but only 3.2 percent of the neurotypical controls, had similar scores.

The researchers say, "The findings illustrate the need for further research to clarify the possible role of autistic traits in the development of chronic depression." In addition, they say, their findings indicate that it might be useful for clinicians to focus on autistic-like social impairments when providing therapy for people with chronic depression.

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"Exploring autistic traits in adults with chronic depression: A clinical study," Martina Radtke, Denisa Wieczoreková, Claus Normann, Pavel Humpolicek, Eva-Lotta Brakemeier, Emanuel Bubl, Ludger Tebartz van Elst, and Andreas Riedel, *Research in Autism Spectrum Disorders*, Vol. 65, September 2019, 34-45. Address: Martina Radtke, martina.radtke@uniklinik-freiburg.de.

Gains from intensive early intervention are lasting

A new study from Europe indicates that the gains made by children with autism spectrum disorders (ASD) who receive early and intensive behavioral intervention (EIBI) last at least a decade.

Dean P. Smith and colleagues followed up on 19 adolescents with ASD who had received two years of EIBI beginning around three years of age. After completing the intervention, which was based on the UCLA model, the children attended a variety of schools where they continued to receive interventions based on applied behavior analysis.

The researchers report, "Results showed the participants significantly increased their cognitive and adaptive standard scores during the two years of EIBI, and that these gains were maintained at follow-up, 10 years after the EIBI had ended. Participants also showed a significant reduction in autism symptoms between intake and follow-up. At follow-up, none of the participants had received any additional psychiatric diagnoses, and none were taking any psychotropic medication."

They conclude, "Results indicate that treatment gains achieved in EIBI are maintained into adolescence."

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"Treatment gains from early and intensive behavioral intervention (EIBI) are maintained 10 years later," Dean P. Smith, Diane W. Hayward, Catherine M. Gale, Svein Eikeseth, and Lars Klintwall, *Behavior Modification*, October 16, 2019 (epub prior to print publication). Address: Svein Eikeseth, Department of Behavioral Science, Oslo Metropolitan University, P.O. Box 4, St., Olavs Plass, Oslo N-0130, Norway, seikeset@oslomet.no.

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Anemia in early pregnancy may up child's risk for ASD

Mothers who are anemic during early pregnancy are at increased odds of having a child with an autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), or intellectual disability, according to a new study conducted by researchers in Sweden and the United States.

Aline Marileen Wiegersma and colleagues analyzed data from nearly 300,000 mothers and more than half a million children born in Sweden between 1987 and 2010. The researchers found that, compared to children born to non-anemic mothers or mothers who developed anemia in late pregnancy, children born to mothers with anemia diagnosed before the thirty-first week of pregnancy had a slightly elevated risk of ASD or ADHD and a significantly higher risk of intellectual disability. When comparing siblings born to the same mother, the researchers found that children exposed to early maternal anemia were at higher risk of ASD and intellectual disability compared to unexposed siblings. However, anemia diagnosed after the thirtieth week of pregnancy was not associated with a higher risk for any of the conditions.

"A diagnosis of anemia earlier in pregnancy might represent a more severe and long-lasting nutrition deficiency for the fetus," study coauthor Renee Gardner comments. "Different parts of the brain and nervous system develop at different times during pregnancy, so an earlier exposure to anemia might affect the brain differently compared to a later exposure."

The researchers say that while they could not ascertain the specific causes for the mothers' anemia, iron deficiency is the most common cause of anemia. They note that an estimated 15 to 20 percent of pregnant women suffer from iron deficiency anemia, and they encourage doctors to screen for this problem in early pregnancy.

Editor's note: Anemia can also stem from folate or vitamin B12 deficiencies, both of which have been implicated as possible contributors to autism.

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"Association of prenatal maternal anemia with neurodevelopmental disorders," Aline Marileen Wiegersma, Christina Dalman, Brian K. Lee, Håkan Karlsson, and Renee M. Gardner, *JAMA Psychiatry*, September 18, 2019 (free online). Address: Renee M. Gardner, Department of Public Health Sciences, Karolinska Institutet, Stockholm SE-171 77, Sweden, renee.gardner@ki.se.

—and—

"Early maternal anemia tied to intellectual disability, ADHD and autism," news release, Karolinska Institutet, August 18, 2019.

Study: Popular tool for screening toddlers for autism spectrum disorders has low success rate

The most widely used tool for screening toddlers for autism spectrum disorders (ASD) misses many toddlers later diagnosed with the condition while incorrectly identifying ASD in a significant percentage of other children, according to a new study.

Whitney Guthrie and colleagues examined the records of nearly 26,000 toddlers seen in the Children's Hospital of Philadelphia network between January 2011 and July 2015. They found that 91 percent of the children were screened using the Modified Checklist for Autism in Toddlers with Follow-Up (M-CHAT/F). The American Academy of Pediatrics (AAP) recommends using this checklist to screen all toddlers for ASD at their 18- and 24-month checkups.

The researchers found that the M-CHAT/F identified only about 40 percent of children who later received an ASD diagnosis. Moreover, of the children flagged as having ASD, only 15 percent later received an ASD diagnosis, although the majority of the others did have some type of developmental problem.

The researchers also found that children from racial minority groups, from non-English speaking households, and from households with lower median incomes who received Medicaid were less likely to receive screening and more likely to receive a false positive score when they did get screened. In addition, the M-CHAT/F was less accurate for girls than for boys.

Only half of the children were tested twice with the M-CHAT/F, as recommended by the AAP. The children who did get tested at two different ages were more likely to be correctly flagged with ASD.

The researchers note that children who screened positive and did prove to have ASD received an official diagnosis seven months earlier than those who screened negative, indicating that screening may help some children who do have ASD receive treatment earlier.

Guthrie comments, "Although our findings reveal significant shortcomings in current screening tools, we want to be clear that we are not recommending that pediatricians stop universal screening. Instead, clinicians should continue to screen using the M-CHAT/F, while being aware that this screening tool does miss some children with ASD. Any clinical or parental concerns should be taken seriously, and warrant continued surveillance even if a child screens negative on the M-CHAT/F."

She adds, "Pediatricians should also be aware of disparities in screening practices and results in children of color and from low-income backgrounds."

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"Accuracy of autism screening in a large pediatric network," Whitney Guthrie, Kate Wallis, Amanda Bennett, Elizabeth Brooks, Jesse Dudley, Marsha Gerdes, Juhi Pandey, Susan E. Levy, Robert T. Schultz, and Judith S. Miller, *Pediatrics*, September 2019 (online). Address: Whitney Guthrie, Children's Hospital of Philadelphia, Roberts Pediatric Research Building, 2716 South Street, 5th floor, Philadelphia, PA 19146, guthriew@email.chop.edu.

—and—

"First large-scale study of universal screening for autism raises critical questions about accuracy, equity," news release, Children's Hospital of Philadelphia, September 27, 2019.

—and—

"Standard screen misses majority of toddlers with autism," Lauren Schenkman, Spectrum News, September 27, 2017.

Researchers question "extreme male brain" theory of autism

The extreme male brain theory of autism, first advanced by Simon Baron-Cohen, proposes that elevated prenatal exposure to androgens ("male" hormones) masculinizes the developing brain, leading to reductions in empathy. A new large-scale study casts doubt on the theory, but some researchers are questioning the validity of the study's findings.

The study, by Amos Nadler and colleagues, involved two groups of neurotypical men. In the first part of the study, 243 men who received either transdermal testosterone gel or a placebo completed a test called the "Reading the Mind in the Eyes Test" (RMET). In the second part of the study, 400 men completed the RMET after receiving either nasal testosterone gel or a placebo.

The researchers also measured all participants' 2D:4D ratio—that is, the relative lengths of the index and ring fingers. In both men and people with autism, the ring finger tends to be longer than the index finger, and researchers speculate that this is due to prenatal exposure to testosterone.

The researchers detected no effect of testosterone administration on RMET scores. In addition, they say, there was no relationship between RMET scores and 2D:4D ratio. Nadler concludes, "Our results unequivocally show that there is not a linear causal relation between testosterone exposure and cognitive empathy."

However, researcher Punit Shah—who was not a part of the study—argues that "there is a critical flaw in the study which undermines the authors' conclusions. The authors used a so-called 'empathy test' that is not a test of empathy at all. The RMET, as used by the authors, has recently been found to be a measure of emotion processing or even just a vocabulary test as it involves knowledge of complex words."

Baron-Cohen also questioned the findings because all of the participants were male rather than female. To detect an effect of testosterone, he argues, it is necessary to study people whose baseline levels are relatively low.

—

"Does testosterone impair men's cognitive empathy? Evidence from two large-scale randomized controlled trials," Amos Nadler, Colin F. Camerer, David T. Zava, Triana L. Ortiz, Neil V. Watson, Justin M. Carré, and Gideon Nave, *Proceedings of the Royal Society B*, August 12, 2019 (free online). Address: Gideon Nave, gnave@wharton.upenn.edu.

—and—

"Extreme male brain theory of autism overturned as huge study finds no link between testosterone and lack of empathy," Kashmira Gander, *Newsweek*, August 3, 2019.

—and—

"Study challenges idea that autism is caused by an overly masculine brain," Emily Underwood, *Science*, September 3, 2019.

Participants needed for ASD microbiome study

Researchers at Massachusetts General Hospital, Harvard Medical School, and the Autism Research Institute are investigating whether the reason why boys are more affected than girls is related to differences in intestinal bacteria.

We are seeking families to participate in this study who have boy and girl siblings with autism. These families will be mailed stool kits with instructions and will be asked to collect samples. A brief medical history will be taken.

For additional information and enrollment details, please contact Harland Winter, MD by phone 617-724-2004 or by email at GenderDimorphism@autism.com.

Survey reveals that pain is common in children with ASD

Children with autism spectrum disorders (ASD) are twice as likely as other children to experience pain, according to a new study.

Daniel Whitney and Danielle Shapiro analyzed data from the 2016-2017 National Survey of Children's Health. The data was collected from the parents of nearly 1,200 children with ASD, more than 300 children with ASD and at least one developmental comorbidity, and nearly 49,000 other children.

The researchers report that the prevalence of pain was 8.2% for children without ASD, 15.6% for children with ASD, and 19.9% for children with ASD and at least one developmental comorbidity. They say, "These findings may be due to several factors, including underlying sensory sensitivities, comorbidity of conditions associated with pain (e.g., cerebral palsy, genetic syndromes impacting gastrointestinal and other systems), and, by extension, a higher frequency of medical procedures that can lead to short-term or long-term pain."

Shapiro notes that children with ASD may react to pain by becoming irritable or exhibiting behavior problems. "A sudden, otherwise unexplained change in behavior is a good clue that something physical, like pain, may be a factor," she says.

Whitney and Shapiro say their findings suggest the need for better awareness of pain in individuals with ASD, better methods for assessing it, and the incorporation of pain management as part of regular therapy for children with ASD.

—

"National prevalence of pain among children and adolescents with autism spectrum disorders" (letter), Daniel G. Whitney and Danielle N. Shapiro, *JAMA Pediatrics*, October 28, 2019 (online). Address: Daniel G. Whitney, Department of Physical Medicine and Rehabilitation, Michigan Medicine, University of Michigan, 325 E. Eisenhower Pkwy, Ann Arbor, MI 48108, dgwhit@umich.edu.

—and—

"Kids with autism are twice as likely to experience pain," Steven Reinberg, HealthDay News, October 28, 2019.

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Eric Hollander, M.D.

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GLUTEN-FREE/CASEIN-FREE DIETS—RESEARCH UPDATES
Kelly Barnhill, MBA, CN, CNN

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RESEARCH UPDATES: THE ROLE OF NEUROTRANSMITTERS IN GI DISORDERS RELATED TO ASD
Kara Gross Margolis, M.D.

—April 15, 2020—
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RESEARCH FINDS GI ISSUES COINCIDE WITH PROBLEM BEHAVIORS IN ASD
Bradley Ferguson, Ph.D.

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High rate of obesity in ASD detcted by meta-analysis

Children with ASD are significantly more likely to be obese than their neurotypical peers, according to a recent meta-analysis.

In the research, Chanaka Kahathuduwa and colleagues analyzed data from multiple studies reporting the prevalence of overweight and/or obesity in children with ASD and matched groups of neurotypical children. The researchers report, "Among children with autism spectrum disorders, the prevalence of obesity was 22.2%. Children with ASD had a 41.1% greater risk of development of obesity."

They add, "Taken together, non-Caucasian race, increasing age, female sex, and living in the United States emerged as potential risk factors for overweight and/or obesity in children with ASD." However, they note, "Caution is advised when interpreting these findings, because [the] findings… are only associational and not causal."

The researchers say many factors may contribute to weight problems in children with ASD. These include genetic effects; prenatal exposure to certain infections, medications, or toxins; maternal diabetes or obesity; intra-uterine growth retardation; and prematurity. In addition, they say, the restricted diets or physical limitations of many children with ASD, as well as treatment with anti-psychotic drugs (which promote weight gain), can play a role.

Kahathuduwa comments, "Neurobehavioral abnormalities related to autism and, more importantly, our treatment decisions may contribute to excessive weight gain in children with autism. Clinicians as well as parents need to be made aware of this greater risk to prevent our children with autism from being victims of obesity and its devastating complications."

—

"The risk of overweight and obesity in children with autism spectrum disorders: a systemic review and meta-analysis," Chanaka N. Kahathuduwa, Blake D. West, Jessica Blume, Nagaraju Dharavath, Naima Moustaid-Moussa, and Ann Mastergeorge, *Pediatric Obesity*, 2019, 1-13. Address: Chanaka Kahathuduwa, Department of Laboratory Sciences and Primary Care, Texas Tech University Health Sciences Center, 3600N Garfield, Midland, TX 79705, chanaka.kahathuduwa@ttuhsc.edu.

—and—

"Autism spectrum disorders linked with excess weight gain in children," news release, Wiley News Room, October 9, 2019.

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ARI'S WORK INCLUDES:

Conducting and sponsoring research on the causes of and best treatments for autism (more than $200,000 in research grants awarded last year), with a focus on research that can translate rapidly into help for today's autistic children and adults and their families.

•

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