

Autism Research Review

I N T E R N A T I O N A L

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Reviewing biomedical and educational research in the field of autism and related disorders

Possible fat-related biomarker detected in very young children with autism spectrum disorders

Researchers in Japan report that they have identified a possible biomarker for autism spectrum disorders (ASD) in very young children.

Noting that both low birth weight and obesity in infancy are known risk factors for ASD, Motoko Maekawa and colleagues hypothesized that ASD may involve abnormal fat-cell metabolism. This led them to

The researchers suggest that FABP4 abnormalities occur during a critical period of early brain development—and that low FABP4 may thus be a factor contributing to ASD rather than simply being a byproduct of the disorder.

investigate levels of adipokines—molecules, some of which affect brain activity, that are secreted by fat cells—in individuals with ASD and neurotypical controls.

First, the researchers compared adipokine levels in blood samples from 123 children with ASD and 92 neurotypical controls. In addition to investigating adipokines already linked to ASD, they measured levels of another adipokine called FABP4. They focused on FABP4 because they had previously found abnormally low levels of this adipokine in the hair follicles of people with schizophrenia.

The researchers say that while levels of other adipokines did not differ between children with ASD and controls, levels of FABP4 were significantly lower in preschool-aged children in the ASD group than in age-matched controls. Repeating the test with a separate group of preschool-aged children, they obtained the same results. Maekawa comments, “The identification of FABP4 as a biomarker that can detect ASD in four- to six-year-old children is good news, especially because early diagnosis and intervention can lead to better long-term prognosis.”

Interestingly, when the researchers measured FABP4 in older children and in postmortem brain tissue samples, they saw no difference between people with and without ASD. This suggests, they say, that FABP4 abnormalities occur during a critical period of early brain development, and that low FABP4 may thus be a factor contributing to

ASD rather than simply being a byproduct of the disorder.

Next, the researchers created mice lacking the FABP4 gene. Compared to control mice, these mice exhibited learning and social problems similar to those seen in individuals with ASD. The neurons in the brains of the mice also exhibited structural characteristics similar to those seen in the postmortem brain tissue samples from individuals with ASD.

Maekawa says, “We hope to replicate our findings in a larger group, which will allow us to determine whether specific ASD symptoms or their severity are related to low levels of FABP4. We also hope to conduct a prospective cohort study of newborns to determine if FABP4 levels at birth can predict the future manifestation of ASD.”

A potential role of fatty acid binding protein 4 in the pathophysiology of autism spectrum disorder,” Motoko Maekawa, Tetsuo Ohnishi, Manabu Toyoshima, Chie Shimamoto-Mitsuyama, Kei Hamazaki, Shabeesh Balan, Yuina Wada, Kayoko Esaki, Shu Takagai, Kenji J Tsuchiya, Kazuhiko Nakamura, Yasuhide Iwata, Takahiro Nara, Yoshimi Iwayama, Tomoko Toyota, Yayoi Nozaki, Hisako Ohba, Akiko Watanabe, Yasuko Hisano, Shigeru Matsuoka, Masatsugu Tsujii, Norio Mori, Hideo Matsuzaki, and Takeo Yoshikawa, *Brain Communications*, September 2020 (online). Address: Motoko Maekawa, Laboratory for Molecular Psychiatry, RIKEN Center for Brain Science, 2-1 Hirosawa, Wako-city, Saitama 351-0198, Japan, motoko.maekawa@riken.jp.

—and—
“FABP4: Preschool-aged biomarker discovered for autism spectrum disorder,” news release, RIKEN Center for Brain Science, September 10, 2020.

Restless legs syndrome may often underlie insomnia in ASD

A new study suggests that sleep problems in children with autism spectrum disorders (ASD) may frequently stem from a condition known as restless leg syndrome (RLS).

Restless leg syndrome causes unpleasant sensations in the legs that lead to an overwhelming urge to move them. The symptoms are strongest in late afternoon and at night, and are most severe when people are resting.

RLS affects 7% to 10% of the general population and is considered to be a neurological sensory disorder. The syndrome appears to be related to dysfunction of dopamine pathways in the basal ganglia. While the cause is unknown in most cases, the condition is genetically influenced and one known risk factor is iron deficiency.

In the new study, Michelle Kanney and colleagues conducted a chart review of 103 children diagnosed with ASD and chronic insomnia and seen at their sleep center. Patients underwent clinical assessment as well as an overnight sleep study and measurement of their iron levels.

The researchers say that 41 of the children were diagnosed with RLS, and diagnosis of RLS was associated with significantly lower serum ferritin (iron) levels. They add, “The presence of leg kicking, body rocking, or

any symptoms involving the legs highly correlated with the diagnosis of RLS.”

The researchers add that nearly all of the children responded positively to treatment. Interventions included iron supplementation (given to 25 children, with 23 improving), the anticonvulsant gabapentin (given to 12

Kanney and colleagues say that of the children diagnosed with insomnia due to restless legs syndrome, nearly all improved with treatment.

children, all of whom improved), or combination therapy (given to 3 children, all of whom improved). They conclude, “Initial assessment [of sleep problems in individuals with ASD] should include a thorough query of behaviors related to nocturnal motor complaints, because RLS may be a treatable cause of sleep disruption.”

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“Rethinking bedtime resistance in children with autism: is restless legs syndrome to blame?,” Michelle L. Kanney, Jeffrey S. Durmer, Lynn Marie Trotti, and Roberta Leu, *Journal of Clinical Sleep Medicine*, August 17, 2020 (online). Address: Michelle Kanney, Emory University School of Medicine and Children’s Healthcare of Atlanta-Egleston Campus, Atlanta, Georgia 30322.

Oxytocin may cause long-term amygdala changes, improvements in social functioning in ASD

A new study from Belgium indicates that administering intranasal doses of the hormone oxytocin to adult men with autism spectrum disorders (ASD) may result in long-term improvements in social functioning as well as changes to regions of the brain involved in emotion.

The double-blind, randomized, placebo-controlled study, conducted by Sylvia Bernaerts and colleagues, included 38 men with ASD, ranging in age from 18 to 35 years. In the study, the researchers measured:

- The immediate effects of a single dose of intranasal oxytocin.
- The short- and long-term effects of multiple doses of intranasal oxytocin taken daily for four weeks.

To measure the effects of oxytocin administration, the researchers asked participants to engage in an emotion processing task while undergoing functional magnetic resonance

Meta-analysis indicates that facial recognition is a significant problem in ASD

Individuals with autism spectrum disorders (ASD) have significant impairments in facial recognition, according to a recent meta-analysis.

Jason Griffin and colleagues analyzed data from 112 studies conducted over the past 40 years. The researchers say, “Our findings indicate that people with ASD struggle to process information about the identity of a face. This deficit is large, such that on average 80.5% of ASD individuals perform worse than typical individuals on tests of face identity processing. This impairment likely contributes to ASD-specific difficulties with social interaction, which requires the ability to identify social partners as unique individuals.”

Study coauthor Suzy Scherf comments, “When someone we know doesn’t recognize us, it can generate a negative reaction. With this finding about poor face recognition skills in autism, people can be more understanding and provide autistic individuals with supports to assist in their social interactions.”

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“A quantitative meta-analysis of face recognition deficits in autism: 40 years of research,” J. W. Griffin, R. Bauer, and K. S. Scherf, *Psychological Bulletin*, October 2020 (online). Address: Suzy Scherf, Department of Psychology, 113 Moore Building, Pennsylvania State University, University Park, PA 16802, suzyscherf@psu.edu.

—and—
“People with autism may have large deficits in facial recognition, news release, Pennsylvania State University, October 28, 2020.

imaging. They also assessed the men’s social functioning and repetitive behaviors before and after treatment.

Bernaerts and colleagues found that oxytocin administration resulted in attenuation of activity in the amygdala, which is part of the brain’s threat-processing circuit. This attenuation was significant four weeks after the treatment and one full year later.

Furthermore, the researchers say, their analysis showed that “participants with stronger attenuations in amygdala activity showed greater behavioral improvements, particularly in terms of self-reported feelings of avoidant attachment and social functioning.” Improvements in repetitive behavior were also seen.

The researchers also detected an increase

in activity of the posterior superior temporal sulcus (pSTS), which is involved in socio-communicative processing, in response to the single dose of oxytocin. However, they say that “no consistent long-term changes in pSTS activity were induced after the multiple-dose treatment.”

“Together,” the researchers say, “these findings indicate that a four-week intranasal oxytocin treatment can induce long-lasting neural changes in core social brain regions.”

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“Oxytocin treatment attenuates amygdala activity in autism: a treatment-mechanism study with long-term follow-up,” Sylvia Bernaerts, Bart Boets, Jean Steyaert, Nicole Wenderoth, and Kaat Alaerts, *Translational Psychiatry*, November 2020 (free online). Address: Kaat Alaerts, kaat.alaerts@kuleuven.be.

Study suggests that epidurals may slightly increase ASD risk

Epidural analgesia given to women during vaginal delivery may slightly increase the risk of autism spectrum disorders (ASD) in their children, according to a new study.

Chunyuan Qiu and colleagues examined data on 147,895 children delivered vaginally either with or without epidural analgesia. The researchers found that 1.9% of the children exposed to epidural analgesia were diagnosed with ASD, compared to 1.3% of unexposed children. The increase in risk remained significant when the researchers controlled for other variables, and it rose with the number of hours of exposure. While women who receive epidural analgesia during long labors have an elevated incidence of fever, controlling for fever did not change the results of the study.

The researchers conclude, “This study suggests that exposure to epidural analgesia for vaginal delivery may be associated with increased risk of autism in children,” adding that additional research is needed to confirm their findings and determine possible mechanisms.

However, several organizations representing anesthesiologists and obstetricians have criticized the study, saying that “an association between a mother’s use of epidural analgesia during childbirth and her infant’s risk of developing autism does not imply causation.” They argue that “if anything, epidurals improve maternal and neonatal outcomes,” stating that “very low levels

of these drugs are transferred to the infant, and there is no evidence that these very low levels of drug exposure cause any harm to an infant’s brain.”

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“Association between epidural analgesia during labor and risk of autism spectrum disorders in offspring,” Chunyuan Qiu, Jane C. Lin, Jiachao M. Shi, Ting Chow, Vimal N. Desai, Vu T. Nguyen, Robert J. Riewerts, R. Klara Feldman, Scott Segal, and Anny H. Xiang, *JAMA Pediatrics*, October 12, 2020 (online). Address: Anny H. Xiang, Department of Research and Evaluation, Kaiser Permanente Southern California, 100 South Los Robles Avenue, Pasadena, CA 91101, anny.h.xiang@kp.org.

—and—
“Labor epidurals do not cause autism; safe for mothers and infants, say anesthesiology, obstetrics,” news release, American Society of Anesthesiologists, October 13, 2020.

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.

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EDITORIAL: Stephen M. Edelson, Ph.D.

Autism Research: Paving the Road Ahead

Over the past 50-plus years, research on autism has moved forward, but only at a slow and steady pace. As of today, there are few promising breakthroughs on the horizon.

Currently, of course, the COVID-19 pandemic is hampering scientific investigation, and many scientists are struggling to keep the integrity of their research projects at the highest possible level. (For more on this, see “COVID 19 and Autism Research: Perspectives from Around the Globe,” *Autism Research*, 2020 June; 13(6): 844-869.)

However, as research begins to regain momentum next year, it is time for stakeholders in the autism community to re-examine the modest advancements of autism research over the past five decades and question the typical “silo” approach used up to now. It is becoming increasingly clear that a better approach is to look at the individual with autism as a whole, and not just focus on one neurological impairment, genetic expression, sensory system, cognitive or social uniqueness, or behavior.

Over the past two years, a number of my editorials in the *Autism Research Review International* have addressed this proposed new approach. In this editorial, I would like to review the research blueprint I have laid out and discuss how the Autism Research Institute (ARI) is taking the initial steps to put it in motion.

Genetics

In his 1964 seminal book, *Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior*, Dr. Bernard Rimland conducted the first meta-analysis in the autism research literature and concluded that genetics play an important role. In this book, in addition to his 1968 film, *The Invisible Wall*, Dr. Rimland argued that the environment may also be a significant contributor.

Today, there has been a tremendous amount of research on genetics, and a growing amount on environmental toxicants, but few studies have investigated their interaction. If one of the primary goals of autism research is to identify causes of autism, then in-depth research on the interaction between genetics and the environment is an obvious avenue to pursue.

Assessment and diagnosis

Because there is no one symptom or behavior that defines autism, an autism diagnosis depends on observed and reported symptoms and behaviors associated with an agreed-upon set of traits. However, several studies have questioned the validity of

the Modified Childhood Autism Checklist (MCHAT), which is the most widely administered screening tool. In one large-scale study published last year and involving nearly 26,000 cases, the results showed an accuracy rate of less than 40%.

Until a set of biomarkers is well-documented, screening and diagnosis should also include the identification of prevalent medical comorbidities. These include anxiety, estimated to occur in as many as 84% of individuals with autism; gastrointestinal disease, estimated to occur in as many as 90%; and sleep disturbances, estimated to occur in as many as 80%. If such medical conditions are identified early on, diagnosis will be more accurate. Moreover, these individuals can receive necessary treatment whether or not they have autism.

Subtyping the autism spectrum

There is mounting evidence that autism is not a true spectrum and does not mirror a normal distribution. Instead, we are beginning to identify distinct autism subtypes based on genetics, neural structure, biochemistry, and sensory sensitivities.

Once subtypes are clearly defined, researchers will be better able to pinpoint environmental contributors to autism. These may include toxicants such as pesticides, hydrocarbons, air pollutants, and heavy metals, all of which have been found to be elevated in many individuals with autism. In time, genetic counseling will be more accurate and will include recommendations on reducing exposure to toxins that impact genetic expression, impair neural structures, alter biochemistry, and affect internal and external sensory organs. In addition, clinicians will be better able to determine the most effective treatments for each autism subtype.

Multidisciplinary treatment

There are many approaches to treating autism, including behavioral, biomedical, medical, neurological, nutritional, and sensory interventions. Different clinicians usually rely on quite different interventions to treat the same challenging behaviors. However, a single approach to treatment will not be optimally effective for all individuals on the autism spectrum.

A much better approach is to conduct multiple evaluations in order to take different perspectives into account. For example, many individuals with autism engage in eye-poking behavior. There are several possible reasons for this behavior, including discomfort or pain in the eye, calcium deficiency, or a desire for

positive attention from others. Assessing a behavior such as this from multiple angles is likely to reveal the true underlying reason and the most effective treatment.

Standardized care

Autism was first described more than 75 years ago, and research on treatments has been ongoing for more than 50 years. However, while there are numerous articles suggesting best practices, there is no accepted standard of care agreed upon by all in the autism community. It is time for us to come together to formulate an extensive treatment protocol that will empower clinicians to provide the best care for individuals with autism.

One way to accomplish this goal is to use valid assessment tools and carefully monitor the effects of various interventions. This will require researchers and clinicians to work together to gather enough data to develop highly accurate statistical formulas, or algorithms, that can determine with high accuracy the most appropriate treatments for each individual.

How ARI is promoting a new era of progress

Earlier this year, ARI began to expand its network of parent support groups worldwide. As of today, there are 100 group members in 44 different countries who have joined ARI's global network. Currently, we are sharing up-to-date research findings that these participants can disseminate to their members. We have also begun to cosponsor webinars with the help of many top experts in the field.

In 2021, we will begin to establish a global researcher network. This network will promote the sharing of information across all fields of study. We also plan to sponsor numerous online meetings to inform the scientific community about promising areas of research, as well as to discuss critical research issues such as genetics, environmental factors, gastrointestinal disease, nutrition, medical comorbidities, and interoceptive sensitivities. In addition, we will inform researchers of grant opportunities available from public agencies and private foundations.

We appreciate any and all support for these initiatives from those on the autism spectrum, their family members, practitioners, researchers, and organizations serving the autism community. I believe that as we begin to work together on a global basis, we will leave “slow and steady” behind and enter an exciting new era of rapid progress that will revolutionize the autism field.

Research Updates

NAC supplementation may improve some symptoms

A recent meta-analysis of five studies suggests that supplementation with N-acetylcysteine (NAC)—the supplement form of the amino acid cysteine—may improve some symptoms in individuals with autism spectrum disorders (ASD).

Pooling results from four of the studies, Tsung-Min Lee and colleagues found that NAC supplementation for 8 to 12 weeks resulted in improvements in total score on the Aberrant Behavior Checklist. Pooled results from three trials showed significant improvements in hyperactivity and irritability, and pooled results from two trials showed improvements in social awareness.

The researchers conclude that “NAC is safe and tolerable, reduces hyperactivity and irritability, and enhances social awareness in children with ASD.”

The researchers believe NAC benefits individuals with autism by helping to correct abnormalities of the glutaminergic system, which are implicated in autism.

“Effectiveness of N-acetylcysteine in autism spectrum disorders: a meta-analysis of randomized controlled trials,” Tsung-Min Lee, Kuan-Min Lee, Chuan-Ya Lee, Hsin-Chien Lee, Ka-Wai Tam, and Wui Loh, *Australian and New Zealand Journal of Psychiatry*, September 8, 2020 (online). Address: El-Wui Loh, Center for Evidence-Based Health Care and Shared Decision Making Resource Center, Department of Medical Research, Taipei Medical University Shuang Ho Hospital, No. 291, Zhongzheng Rd., Zhonghe District, New Taipei City 23561, Taiwan, lohewui@tmu.edu.tw.

Few individuals with ASD get full genetic testing

Only about 3% of individuals with autism spectrum disorders (ASD) receive a full genetic screening, according to a new study.

Daniel Moreno-De-Luca and colleagues analyzed medical records and personal reports for 1,280 individuals with ASD, focusing on the time period of April 2013 to April 2019. Participants were enrolled in a study by the Rhode Island Consortium for Autism Research and Treatment.

Moreno-De-Luca and colleagues note that medical associations including the American Academy of Pediatrics, the American College of Medical Genetics, and the American Academy of Child and Adolescent Psychiatry recommend providing both chromosomal microarray testing and Fragile X testing for patients diagnosed with ASD. The researchers found that 16.5% of the participants had received some testing, with

13.2% being tested for Fragile X and 4.5% getting chromosomal testing. However, only 3% of the individuals were reported to have received both tests.

While the researchers note that young people with ASD were more likely to be fully tested than older individuals, Moreno-De-Luca says their study “underscores that there is still significant work to be done, especially for adults on the autism spectrum.”

“Clinical genetic testing in autism spectrum disorder in a large community-based population sample,” Daniel Moreno-De-Luca, Brian C. Kavanaugh, Carrie R. Best, Stephen J. Sheinkopf, Chanika Phornphutkul, and Eric M. Morrow, *JAMA Psychiatry*, Vol. 77, No. 9, September 2020 (free online). Address: Eric Morrow, Laboratories for Molecular Medicine, Brown University, 70 Ship St. Box G-E4, Providence, RI 02903, eric_morrow@brown.edu.

“Study finds only 3% of individuals with autism receive recommended genetic tests,” news release, Brown University, May 13, 2020.

PCOS in mothers again linked to problems in kids

Mothers who have polycystic ovarian syndrome (PCOS) have increased odds of having children with psychiatric or neurodevelopmental disorders, according to a large-scale study.

PCOS causes women to overproduce androgens such as testosterone. It is the most common cause of anovulatory infertility (in which the ovaries do not release eggs during the menstrual cycle).

Xinxia Chen and colleagues compared nearly 25,000 Finnish children born to mothers diagnosed with PCOS or anovulatory infertility to more than one million children born to mothers without PCOS. The researchers found that children born to mothers with PCOS had an elevated risk of neurodevelopmental or psychiatric disorders. This risk remained significant when the researchers controlled for the babies’ sex and maternal obesity; however, it was even higher if mothers were severely obese, experienced perinatal problems, experienced gestational diabetes, or had a caesarean delivery.

Having a mother with PCOS increased the risk of intellectual disabilities and ASD 1.4-fold. It also significantly increased the risk of sleeping disorders, attention-deficit hyperactivity disorder (ADHD), conduct disorder, tic disorders, developmental disorders, eating disorders, anxiety, mood disorders, and other behavioral and emotional disorders.

The findings are broadly consistent with the results of several other studies. For instance, in 2018, Adriana Cherskov and colleagues reported that women with autism

have an approximately two-fold increase in risk for PCOS, and women with PCOS have a two-fold increase in rates of autism (see ARRI 2018, No. 4). In 2016, Kyriaki Kosidou and colleagues found that maternal PCOS increased the odds of ASD in children by 59% (see ARRI 2016, No. 4).

“Association of polycystic ovary syndrome or anovulatory infertility with offspring psychiatric and mild neurodevelopmental disorders: a Finnish population-based cohort study,” Xinxia Chen, Linghua Kong, Terhi T. Piltonen, Mika Gissler, and Catarina Lavebratt, *Human Reproduction*, September 1, 2020 (free online). Address: Catarina Lavebratt, Translational Psychiatry Unit, Centre for Molecular Medicine, Karolinska University Hospital, L8:00, 171 76 Stockholm, Sweden, catarina.lavebratt@ki.se.

“PCOS is linked to increased risk of neuro-psychiatric disorders in offspring,” news release, European Society of Human Reproduction and Embryology, September 1, 2020.

Early or late birth tied to small increase in ASD risk

Children born either pre- or post-term have a slightly increased risk for autism spectrum disorders (ASD), according to a large-scale study.

Martina Persson and colleagues analyzed data from medical registries in Sweden, Finland, and Norway. The databases included information on more than 3.5 million children born between 1995 and 2015.

The researchers found that the risk of ASD increased slightly for each week a child was born pre- or post-term. This risk was independent of sex and birth weight for gestational age. Persson and colleagues note, “The risk of ASD was not confined to the pre- or post-term periods but was also higher during weeks of gestation commonly included in the definition of ‘term’ birth, i.e., [there was a] higher risk at individual gestational weeks immediately below and above week 40. This is in line with the shape of risk patterns reported for other neurological outcomes, including cerebral palsy and cognitive ability (IQ).”

“Gestational age and the risk of autism spectrum disorder in Sweden, Finland, and Norway: a cohort study,” Martina Persson, Signe Opdahl, Kari Risnes, Raz Gross, Eero Kajantie, Abraham Reichenberg, Mika Gissler, and Sven Sandin, *PLOS Medicine*, September 22, 2020 (free online). Address: Martina Persson, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, Martina.Persson@ki.se.

“Small increase in risk of autism seen for pre- and post-term births,” news release, Public Library of Science, September 22, 2020.

Research Updates

Early puberty a common finding in girls with ASD

Girls with autism spectrum disorders (ASD) tend to enter puberty at an earlier age than neurotypical girls, according to a new study.

Blythe Corbett and colleagues analyzed data from 239 children between 10 and 13 years of age. Of the children, 137 were diagnosed with ASD while 102 were neurotypical controls. The group with ASD included 35 females and 102 males.

Measuring the onset of puberty based on the development of genitalia and pubic hair, the researchers found “significantly earlier pubertal development in females with ASD but not males.” Autistic girls tended to start puberty about nine and a half months earlier than neurotypical girls. In addition, girls with ASD had an earlier onset of menstruation than neurotypical girls.

In an interview with *Spectrum News*, Corbett notes that the changes that accompany puberty can be challenging for girls with ASD, saying “We need to better prepare, educate and support youth with autism during the pubertal transition. This is especially true for girls with autism who are showing earlier menses and breast development.... We need to better prepare young women with knowledge of the physical, sensory and emotional changes they will experience and normalize these changes. We also need to recognize that youth with autism may benefit from psychological and sexual education about the many changes in adolescence.”

“Pubertal timing during early adolescence: advanced pubertal onset in females with autism spectrum disorder,” Blythe A. Corbett, Simon Vandekar, Rachael A. Muscatello, and Yasas Tanguturi, *Autism Research*, October 12, 2020 (epub prior to print publication). Address: Blythe Corbett, PMB 40, 230 Appleton Place, Nashville, TN, 37203, blythe.corbett@vumc.org.

“Puberty may arrive early for some autistic girls,” Taylor White, *Spectrum News*, October 27, 2020.

Exercises that are similar to stereotyped behaviors are most effective in reducing these behaviors

A new study from China indicates that while physical exercise can help reduce stereotypic behaviors in children with autism spectrum disorders (ASD), it is important to select exercises that are similar to the behaviors.

In earlier research involving 30 children with ASD, C. Y. Andy Tse and colleagues examined the effects of a ball-tapping exercise on stereotypic behaviors. In the ball-tapping exercise, participants were asked to tap a playground ball as many times as they could for 15 minutes. The researchers found that compared to a control activity (story time), the ball-tapping exercise resulted in significant reductions in hand flapping but not in body rocking.

In a new study involving 21 children with ASD, the researchers compared the effects of ball-tapping and jogging on stereotypic behaviors. This time, the children participated in the ball-tapping activity one day, jogged one day, and spent one day in the control group. The schedule was randomized so the children did not all do the activities in the same order.

The researchers report, “Results revealed that only hand-flapping stereotypic behaviors were significantly reduced in the ball-tapping exercise, while only body-rocking stereotypic behaviors were significantly reduced in the jogging exercise condition.” Reductions in stereotypic behavior lasted approximately 45 minutes.

The researchers conclude, “Physical exercise should be topographically matched with stereotypic behavior in order to produce desirable behavioral benefits in children with ASD.”

“Investigating the matching relationship between physical exercise and stereotypic behavior in children with autism,” Andy C. Y. Tse, Venus H. L. Liu, and Paul H. Lee, *Medicine and Science in Sports and Exercise*, September 25, 2020 (epub prior to print publication). Address: Andy C. Y. Tse, Department of Health and Physical Education, The Education University of Hong Kong, Hong Kong, China, andytcy@eduhk.hk.

—see also—

“Choosing an appropriate physical exercise to reduce stereotypic behavior in children with autism spectrum disorders: a non-randomized crossover study,” C. Y. Andy Tse, C. L. Pang, and Paul H. Lee, *Journal of Autism and Developmental Disorders*, Vol. 48, 2018, 1666-1672. See address above.

Vitamin D supplementation may be beneficial in ASD

Giving vitamin D supplements to children with autism spectrum disorders (ASD) may improve their symptoms, according to a new study from Iran.

Zohreh Javadfar and colleagues enrolled 43 children with ASD in the study. The researchers administered vitamin D drops (from 300 IU/kilogram up to 6000 IU/kilogram daily) to approximately half of the group for 15 weeks, while the other half received a placebo.

The researchers evaluated the children’s behavior before and after supplementation using the Childhood Autism Rating Scale (CARS), the Autism Treatment Assessment Checklist (ATEC), and the Aberrant Behavior Checklist-Community (ABC-C). Because vitamin D helps regulate levels of serotonin, which are altered in autism, the researchers also measured the children’s serum levels of serotonin at the beginning and end of the study. In addition, because vitamin D is anti-inflammatory and autism may be associated with elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6), the researchers measured serum IL-6 levels before and after treatment.

At the beginning of the study, more than 86% of the children had a vitamin D deficiency. By the end of the study, however, serum levels of vitamin D had increased significantly in the group getting the vitamin D drops. Scores on both the CARS and ATEC scales improved significantly in this group, and the researchers say that “nearly all symptoms relating to neurodevelopmental defects... were significantly improved following vitamin D supplementation.” However, there was no change in the children’s levels of serotonin or IL-6, and no change on the ABC-C.

The researchers conclude, “These findings suggest that vitamin D supplementation may improve ASD symptoms; however, more studies with longer duration are indispensable to confirm our results.”

“Effects of vitamin D supplementation on core symptoms, serum serotonin, and interleukin-6 in children with autism spectrum disorders: a randomized clinical trial,” Zohreh Javadfar, Hadi Abdollahzad, Jalal Moludi, Shahab Rezaeian, Houshang Amirian, Ali Akbar Foroughi, Seyed Mostafa Nachvak, Nasrin Goharmehr, and Roghayeh Mostafai, *Nutrition*, Vol. 79-80, November-December 2020 (online). Address: Corresponding author: Dr. Hadi Abdollahzad, Department of Nutritional Sciences, School of Nutritional Sciences and Food Technology, Kermanshah University of Medical Sciences, Kermanshah, Iran, hadi_nut@yahoo.com.

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<https://www.autism.org/finding-a-clinician/>

Bullying significantly increases suicidality in teens with ASD

Bullying is a significant risk factor for suicidal thoughts and behaviors in teenagers with autism spectrum disorders (ASD), according to a new study.

In the study, Rachel Holden and colleagues reviewed the clinical records of 680 teens with ASD who were referred to a mental health clinic, focusing only on teens who initially were not suicidal. To zero in on the effects of bullying, they controlled for the presence of co-occurring psychiatric conditions and a number of other sociodemographic and clinical factors.

In the initial visits, nearly one-third of the teenagers reported being bullied. The researchers report, “We found that if [teenagers] reported being bullied in the first month after they were first seen by mental health services, they were nearly twice as likely to go on to develop suicidal thoughts or behaviors.”

The effects of bullying were much stronger for females than for males. They were

ASD, ADHD associated with more early medical visits

Children with autism spectrum disorders (ASD) and/or attention deficit hyperactivity disorder (ADHD) tend to have significantly more medical visits during infancy than other children, according to a new study.

In the study, Matthew Engelhard and colleagues analyzed 10 years of data collected from the electronic health records of nearly 30,000 patients who had at least two well-child visits before they were one year of age. The researchers found that children later diagnosed with ASD and/or ADHD tended to have longer hospital stays compared to other children. Children with ASD had higher numbers of procedures such as intubation and ventilation, as well as more outpatient visits for services such as physical therapy and eye exams. Children with ADHD had more procedures and more hospital admissions and emergency department visits.

Engelhard says, “This study provides evidence that children who develop autism and ADHD are on a different path from the beginning.” He notes that identifying patterns of health care utilization could aid clinicians in spotting children at risk for these disorders.

“Health system utilization before age 1 among children later diagnosed with autism or ADHD,” Matthew M. Engelhard, Samuel I. Berchuck, Jyotsna Garg, Ricardo Henao, Andrew Olson, Shelley Rusincovitch, Geraldine Dawson, and Scott H. Kollins, *Nature Scientific Reports*, October 2020 (free online). Address: Matthew Engelhard, m.engelhard@duke.edu.

—and—

“Children with autism, ADHD have more doctor and hospital visits during infancy,” news release, Duke University Medical Center, October 19, 2020.

also stronger for teens who had a diagnosis of psychosis or affective disorder and for teens with high IQs. However, the effects of bullying remained significant even after the researchers controlled for these factors.

Holden and coauthor Johnny Downs comment in *Spectrum News*, “We urge clinicians to... make a concerted effort to ask children with autism about bullying. And when a young autistic person reports bullying to mental health professionals, it needs to be taken seriously.”

In addition, they say, “Teachers have a key role to play. In school settings, evidence suggests that intensive anti-bullying interventions in which teachers meet with parents are most effective. Schools can also benefit from autism-specific anti-bullying strategies, including ‘befriending interventions,’ which help autistic children form friendships with typical peers. Schools should use robust evaluations to assess the effectiveness of such interventions and involve young people with autism in the development of their anti-bullying policies.”

“Investigating bullying as a predictor of suicidality in a clinical sample of adolescents with autism spectrum disorder,” Rachel Holden, Joanne Mueller, John McGowan, Jyoti Sanyal, Maxim Kikoler, Emily Simonoff, Sumithra Velupillai, and Johnny Downs, *Autism Research*, June 2020 (online). Address: Johnny Downs, Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, Box PO84 16 De Crespigny Park, London SE5 8AF, UK, johnny.downs@kcl.ac.uk.

—and—

“Why it is imperative to ask autistic adolescents about bullying,” Johnny Downs and Rachel Holden, *Spectrum News*, October 6, 2020.

Coping with COVID-19

To aid individuals with autism and their families during the COVID-19 pandemic, ARI is offering these resources:

- Free presentations offering evidence-based strategies to manage at home during extended school closures.
- Social stories and short videos on hygiene and medical procedures.
- Physician resources for supporting patients diagnosed with autism.

To view these, as well as to see first-person stories by families about how they are dealing with this crisis, visit this link:

<https://www.autism.org/covid-19-resources/>

ASD may involve damage to peripheral nerves

A new study from Taiwan suggests that the peripheral nervous system, which is composed of the nerves lying outside the brain and spinal column, may play a role in autism spectrum disorders (ASD).

Yi-Ling Chien and colleagues enrolled 32 men with ASD and 27 neurotypical men and women in the study. All participants underwent tests of their sensory nerves, including skin biopsies to look for damage to the small fibers in the nerves. In addition, the researchers examined the electrical responses of nerves to heat pulses applied to the skin. Participants with ASD also filled out questionnaires about their sensory issues.

The researchers found that 53% of individuals with autism, but no members of the control group, had reduced nerve fiber density. Members of the ASD group who had reduced nerve fiber density tended to feel pain from the heat stimulus at a higher temperature threshold than controls. Study coauthor Sung-Tsang Hsieh says, “This indicates that the nerves have degenerated, similar to what happens for people with the condition of peripheral neuropathy, where the threshold for feeling heat and other sensations is higher than for other people.”

The researchers also found that people with ASD who had normal nerves were more likely to dislike being touched and to be bothered by certain textures, while people with ASD who exhibited nerve fiber damage were more likely to say they liked to go barefoot and to be unaware when they got scratched or bruised.

The researchers conclude, “These observations indicated that a substantial portion of [individuals with ASD] had small fiber pathology, which was associated with tactile and autistic symptoms, providing structural and physiologic evidence for the involvement of peripheral sensory nerves in autism.”

Noting that more than 70% of people with ASD exhibit anomalies in sensory perception, Hsieh says, “If larger studies can confirm these results, it is possible that further insight into the peripheral nervous system could help us understand how this disorder develops and potentially light the way for treating these distressing sensory symptoms that most people with autism experience.”

“Small fiber pathology in autism and clinical implications,” Yi-Ling Chien, Chi-Chao Chao, Shao-Wei Wu, Hsueh-Wen Hsueh, Yen-Nan Chiu, Wen-Che Tsai, Susan Shur-Fen Gau, and Sung-Tsang Hsieh, *Neurology*, October 14, 2020 (online). Address: Susan Shur-Fen Gau, Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan, gaushufe@ntu.edu.tw.

—and—

“Nerves that sense touch may play role in autism,” *Science Daily*, October 14, 2020.

Valproic acid exposure in utero raises risk of ASD, ADHD

Women with epilepsy who take the anticonvulsant drug valproic acid during pregnancy have a significantly elevated risk of having a child with autism spectrum disorder (ASD) or attention-deficit hyperactivity disorder (ADHD), according to a new study.

The study, conducted by Kelsey Wiggs and colleagues, examined data on more than 14,000 children born to women with epilepsy between 1996 and 2011. Nearly one-quarter of the women reported using anticonvulsant medication in their first trimester. The most common drugs the women took were carbamazepine (Tegretol), lamotrigine (Lamictal), and valproic acid (Depacon/Depakene/Stavzor).

After controlling for factors such as the severity of the women's epilepsy, the researchers found that women who reported using valproic acid during their first trimester of pregnancy had a 2.3 times higher risk of

having a child with ASD and a 1.7 times higher risk of having a child with ADHD compared to women with epilepsy who did not take anticonvulsants. There was no increased risk for women who took lamotrigine or carbamazepine.

The researchers conclude, "Our findings add to a growing body of evidence that suggests that certain anti-seizure medications may be safer than others in pregnancy."

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"Anti-seizure medication use during pregnancy and risk of ASD and ADHD in children," Kelsey K. Wiggs, Martin E. Rickert, Ayesha C. Suján, Patrick D. Quinn, Henrik Larsson, Paul Lichtenstein, A. Sara Oberg, and Brian M. D'Onofrio, *Neurology*, October 28, 2020 (free online). Address: Kelsey K. Wiggs, kkwiggs@indiana.edu.

—and—
"Antiseizure medication in pregnancy associated with twice the risk of autism in child," news release, American Academy of Neurology, October 28, 2020.

Standard newborn hearing test may help identify autism

A standard hearing test given routinely to newborns may help doctors identify autism spectrum disorder (ASD), according to new research.

Oren Miron and colleagues analyzed data on nearly 140,000 newborns who underwent the auditory brainstem response (ABR) test, which is typically administered in hospital maternity wards. Of the children, 321 were later diagnosed with ASD. The researchers found that newborns who later received an ASD diagnosis had slower brain responses to sounds during their tests. The differences were especially pronounced in the right ear. These findings, they say, are similar to the findings seen in older infants and children with ASD.

Study co-author Elizabeth Simpson says, "We're not at the point just yet where we're

telling clinicians to use ABR testing as a determinant for autism in babies. But we are saying that this study presents a promising direction in how ABR testing can be used as a method for precise autism detection at birth."

—
"Prolonged auditory brainstem response in universal hearing screening of newborns with autism spectrum disorder," Oren Miron, Rafael E. Delgado, Christine F. Delgado, Elizabeth A. Simpson, Kun-Hsing Yu, Anibal Gutierrez, Guangyu Zeng, Jillian N. Gerstenberger, and Isaac S. Kohane, *Autism Research*, November 2020 (free online). Address: Isaac S. Kohane, Department of Biomedical Informatics, Harvard Medical School, Boston, MA 02115, isaac_kohane@hms.harvard.edu.

—and—
"Hearing test may detect autism in newborns," news release, University of Miami, November 12, 2020.

Free Autism Continuing Education and Webinars

Free Certificates of Participation are available upon passing an online quiz for most webinars. Some events offer Continuing Education Units and/or Continuing Medical Education credits.

—January 6, 2021—
1 p.m. Eastern time

Children, Anxiety, and ASD in the Pandemic Era—Live Q&A
Lauren Moskowitz, Ph.D.

—January 24, 2021—
1 p.m. Eastern time

The Role of Neurotransmitters in GI Disorders Related to Autism
Kara Gross-Margolis, M.D.

Space is limited—watch your email, or visit us on Facebook and Twitter for updates and registration links. You can view previous webinars at <https://www.autism.com/webinars>.

* We are grateful to our friends at the Johnson Center for Child Health & Development for working in partnership to offer presentations.

Impaired gut microbial detoxification seen in ASD

A new study from China suggests that the gut microbes of people with autism spectrum disorders (ASD) are impaired in their ability to detoxify harmful substances, and that this impairment may cause injury to the mitochondria—the "power plants" of cells. Mitochondrial dysfunction is a common finding in ASD.

Mengxiang Zhang and colleagues compared children with ASD and neurotypical controls, using a "quasi-pairing" strategy to compare the children with ASD to controls who would normally have similar gut microbiomes due to factors such as age and place of residence. The researchers analyzed stool samples from 65 ASD/control pairs.

They report, "[O]ur study revealed a previously unidentified ASD-associated deficiency in microbial detoxification, which exhibited a strong correlation with the degree of mitochondrial dysfunction, as well as the severity of clinical manifestations." They hypothesize, "When the intestinal microbial detoxification is severely impaired in ASD, more toxicants of external and internal origins might enter circulation and injure the mitochondria of various tissues. Thus, our finding of impaired microbial detoxification helps explain why ASD children are so vulnerable to environmental toxins and suggests that impairment in microbial detoxification might be involved in the pathogenesis of ASD."

While the researchers note that the reasons for the impairment in microbial detoxification seen in individuals with ASD are not clear, they say, "These findings pave the way for designing future therapeutic strategies to restore microbial detoxification capabilities for patients with ASD."

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"A quasi-paired cohort strategy reveals the impaired detoxifying function of microbes in the gut of autistic children," Mengxiang Zhang, Yanan Chu, Qingren Meng, Rui Ding, Xing Shi, Zuqun Wang, Yi He, Juan Zhang, Jing Liu, Jie Zhang, Jun Yu, Yu Kang, and Juan Wang, *Science Advances*, October 21, 2020 (free online). Address: Juan Wang, wjuan@hsc.pku.edu.cn.

ARI 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.

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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.
Networking researchers, physicians, and parents to speed the development and dissemination of safe and effective treatment methods.
Hosting webinars and one of the largest international websites on autism in the world.
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