Volume 30, No. 1 2016

Autism Research Review INTERNATIONAL

A quarterly publication of the Autism Research Institute—www.Autism.com

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

Prenatal carnitine supplementation may help prevent ASD caused by TMLHE gene mutation

One gene implicated as a contributor to autism—a mutated variant of the TMLHE gene—makes it impossible for cells to manufacture carnitine. New research suggests that for children with this gene, prenatal carnitine supplementation may help prevent autism.

Zhigang Xie and colleagues have refined a technology that allows them to mark, follow, and analyze individual neural stem cells in a developing brain. Studying embryonic mouse brains, they were able to determine that neural stem cells unable to produce carnitine because of a defective TMLHE gene do not function properly.

Normally when neural stem cells divide, they produce two "daughter" cells; one remains a neural stem cell, while the other differentiates. Neural stem cells that are deficient in carnitine frequently produce two differentiated cells instead, failing to resupply the brain with needed neural stem cells.

To see if providing cells with carnitine could correct this abnormality, the researchers incubated fetal forebrain tissue in a medium with or without carnitine. They found that in the presence of carnitine, the cells functioned normally.

The researchers note that the TMLHE gene is located on the X chromosome. Because males have only one X chromosome, while females have two (the second gene could compensate for the mutated one), male children are at greater risk for TMLHE-associated autism.

In addition to manufacturing carnitine, the body obtains it from food. Red meat is very high in carnitine and whole milk is a good source, while vegetables are very low in this nutrient. The researchers speculate that mothers who eat few carnitine-rich foods during pregnancy may put children with the TMLHE gene variant at greater risk for developing autism.

They conclude, "We suggest that genetic screening of prospective parents for TMLHE mutations, coupled with inclusion of carnitine as a dietary supplement upon initial diagnosis of pregnancy, promises mental health benefits for newborns otherwise at significant risk for developmental brain disorders."

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"Inborn errors of long-chain fatty acid β-oxidation link neural stem cell self-renewal to autism," Zhigang Xie, Albert Jones, Jude T. Deeney, Seong Kwon Hur, and Vytas A. Bankaitis, *Cell Reports*, February 9, 2016 (online). Address: Zhigang Xie, zxie@tamhsc.edu.

—and—

"Research hints at a nutritional strategy for reducing autism risk," Christina Sumners, *Vital Record*, Texas A&M Health Science Center, January 28, 2016.

Shank3-related autism reversed in mouse model

About 1% of individuals with autism have a mutation or deletion involving a gene called Shank3. In a new study, researchers found that restoring the function of this gene reversed several symptoms of autism in Shank3-deficient mice.

The Shank3 protein, found in the synapses between neurons, is a scaffold protein that helps to organize other proteins necessary to coordinate a cell's response to incoming signals. Shank3 is found primarily in the striatum, a brain region involved in motor activity, emotional aspects of behavior, and decision-making.

In the new study, Yuan Mei and colleagues genetically engineered mice so their Shank3 gene was turned off during embryonic development but could be turned

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Brain levels of vitamin B_{12} low in autism, schizophrenia

Individuals with autism or schizophrenia have unusually low brain levels of vitamin B_{12}, according to a new study partially funded by the Autism Research Institute.

Yiting Zhang and colleagues measured levels of different forms of cobalamin (vitamin B_{12}) in postmortem brain samples from 12 people with autism, 9 people with schizophrenia, and 43 neurotypical controls. The neurotypical controls ranged in age from 19 weeks of fetal development through 80 years of age.

> Individuals with autism or schizophrenia had levels of methylcobalamin and adenosylcobalamin (two active forms of B_{12}) more than three times lower than those of age-matched neurotypical controls.

The researchers found that in neurotypical controls, levels of total cobalamin dropped dramatically with age. There was a greater than 12-fold decrease in methylcobalamin (an active form of B_{12}) in samples from people between 61 and 80 years of age in comparison to samples from young people.

Individuals with autism had levels of methylcobalamin and adenosylcobalamin (another active form of B_{12}) more than three times lower than those of age-matched neurotypical controls. The average brain level of B_{12} in children with autism was close to levels in brain tissue from neurotypical adults in their 50s. Lower-than-average levels of B_{12} persisted across the lifespan in individuals with autism or schizophrenia.

Study coauthor Richard Deth says, "The large deficits of brain B_{12} from individuals with autism and schizophrenia could help explain why patients suffering from these disorders experience neurological and neuropsychiatric symptoms. These are particularly significant findings because the differences we found in brain B_{12} with aging, autism and schizophrenia are not seen in the blood, which is where B_{12} levels are usually measured."

The researchers say that low levels of B_{12} in autism and schizophrenia may stem from oxidative stress. They recommend research to determine if individuals with autism or schizophrenia could benefit from supplemental vitamin B_{12} and antioxidants.

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"Decreased brain levels of vitamin B_{12} in aging, autism and schizophrenia," Yiting Zhang, Nathaniel W. Hodgson, Malav S. Trivedi, Hamid M. Abdolmaleky, Margot Fournier, Michel Cuenod, Kim Quang Do, and Richard C. Deth, *PLOS ONE*, January 22, 2016 (online). Address: Richard Deth, rdeth@nova.edu.

—and—

"Study: Vitamin B_{12} levels low in brains affected by autism or schizophrenia," Autism Speaks, January 25, 2016.

New study reinforces evidence that low vitamin D contributes to ASD, treatment can help

A new study adds to evidence that vitamin D deficiency or inadequacy is common in children with autism spectrum disorders (ASD), and that improving these children's vitamin D status may reduce their symptoms.

Junyan Feng and colleagues tested the vitamin D levels of 215 children with ASD and 285 neurotypical controls matched for age and sex. They evaluated the children with ASD using the Autism Behavior Checklist (ABC) and Childhood Autism Rating Scale (CARS). Higher scores on these tests indicate increased severity.

The researchers report, "Serum 25(OH) D levels were significantly lower in children with ASD compared with typically developing children." They detected overt deficiency in 13% of the children with ASD, and inadequate vitamin D levels in 71.2%. In comparison, none of the controls were deficient and 61.8% had inadequate levels.

In addition, the researchers report that children with low vitamin D had higher total scores and language scores on the ABC. However, initial CARS scores did not correlate with vitamin D levels.

The researchers recommended supplementation for all of the children with vitamin D deficiency or inadequacy. However, while 181 children in the ASD group had low levels of vitamin D, only 37 caretakers agreed to supplementation and followed through consistently. Children whose parents agreed to treatment received intramuscular vitamin D (150,000 IU every month) and oral vitamin D (400 IU daily) for three months.

After treatment, the researchers report, all of the children had significantly increased vitamin D levels. In addition, they say, total ABC scores, some scores of the ABC subscales (social skills, body and object use, language, and self-help), and total CARS scores were reduced significantly in comparison to pre-treatment scores. The sensory scores on the ABC also exhibited a decreasing trend, although this did not reach significance.

> The researchers conclude, "Supplementation of vitamin D3, which is a safe and cost-effective form of treatment, may significantly improve outcome in some children with ASD, especially in younger children."

The researchers say their findings are consistent with earlier studies indicating that vitamin D levels are lower in children with ASD; that there is an increased prevalence of ASD in darker-skinned children (who absorb less vitamin D from sunshine); and that there is a greater likelihood of ASD in children of mothers who are vitamin D-deficient during pregnancy. In addition, they cite another recent study (Saad et al.) which found that correcting low vitamin D levels in children with ASD led to significant clinical improvements. In that study, more than 80% of 83 children with ASD who received vitamin D treatment improved significantly.

The researchers note that vitamin D is a hormone that is active throughout the body and is "not only important in regulating calcium and phosphate metabolism but also in neurodevelopment, immunological modulation (including the brain's immune system), antioxidation, anti-apoptosis, neural differentiation, and gene regulation."

They conclude, "Supplementation of vitamin D3, which is a safe and cost-effective form of treatment, may significantly improve outcome in some children with ASD, especially in younger children."

(See related article below.)

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"Clinical improvement following vitamin D_3 supplementation in autism spectrum disorder," Junyan Feng, Ling Shan, Lin Du, Bing Wang, Honghua Li, Wei Wang, Tiantian Wang, Hanyu Dong, Xiaojing Yue, Zhida Xu, Wouter G. Staal, and Feiyong Jia, *Nutritional Neuroscience*, January 18, 2016 (epub prior to print publication). Address: Feiyong Jia, Department of Pediatric Neurology and Neurorehabilitation, The First Hospital of Jilin University, No. 71, Xinmin Street, Changchun130021, Jilin Province, China, 458084864@163.com.

—and—

"Vitamin D status in autism spectrum disorders and the efficacy of vitamin D supplementation in autistic children," K. Saad, A. A. Abdel-rahman, Y. M. Elserogy, A. A. Al-Atram, J. J. Cannell, G. Bjørklund, M. K. Abedl-Reheim, H. A. K. Othman, A. A. El-Houfey, N. H. R. Abd El-Aziz, K. A. Abd El-Baseer, A. E. Ahmed, and A. M. Ali, *Nutritional Neuroscience*, April 15, 2015 (epub prior to print publication). Address: Khaled Saad, Khaled.ali@med.au.edu.eg.

Can vitamin D supplementation reduce ASD recurrence rate?

Vitamin D supplementation during prenatal development and early childhood may reduce the risk of autism spectrum disorders (ASD) in siblings of children with the condition, a small study funded by the Autism Research Institute suggests.

Gene Stubbs and colleagues prescribed vitamin D (5000 IU per day) to 19 pregnant women who already had one or more children with autism. All of the women were in their first, second, or early third trimester of pregnancy, and only two of them were overtly deficient in vitamin D before receiving supplementation.

In addition, the researchers supplemented the women's infants with vitamin D (1000 IU per day) from birth to their third birthday. The children were assessed for autism at 18 and 36 months of age.

The researchers say, "The final outcome was 1 out of 19 (5%) developed autism in contrast to the recurrence rate of approximately 20% in the literature." They add, "We also found support for previous studies showing that vitamin D may reduce the incidence of preterm births, small-for-dates, and pre-eclampsia [a serious complication of pregnancy]."

Stubbs and colleagues comment, "Our preliminary impression is that the best outcome for the children of mothers who get pregnant is for the mothers to be vitamin D 'replete' during the periconceptual period, that is, to have the optimal level of vitamin D at least two months before the mother gets pregnant."

The researchers say that while their results are promising, this was a small study with no controls and their results will need to be replicated.

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"Autism: Will vitamin D supplementation during pregnancy and early childhood reduce the recurrence rate of autism in newborn siblings?" G. Stubbs, K. Henley, and J. Green, *Medical Hypotheses*, Vol. 88, 2016 (online). Address: Gene Stubbs, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd., Portland, OR 97239, stubbsgene@comcast.net.

EDITORIAL:
Stephen M. Edelson, Ph.D., Autism Research Institute, and Margaret L. Bauman, M.D., Boston University School of Medicine

Aging in autism: A call to action

Twenty years ago there was much talk but little action about the inevitable onslaught of children and teenagers on the autism spectrum reaching adulthood. Whether it was hesitation or procrastination, private and public agencies delayed planning, and the autism community is now scrambling to figure out ways to best provide needed support and services to young adults on the spectrum. A similar scenario is starting to play out with respect to seniors with autism. Today there is little discussion about individuals with autism reaching their senior years even though three notable individuals on the spectrum have reached this age-related milestone.

Donald T. is considered by many to be the first "official" child to be diagnosed with autism. Donald was case #1 in Dr. Leo Kanner's seminal paper, *Autistic Disturbances of Affective Contact*, published in 1943. Donald, then five years of age, exhibited many of the characteristics often associated with "classical" autism or Kanner's syndrome including a preference to be alone, engagement in repetitive behaviors, echolalia, and an exceptional memory.

Donald is now in his early 80s and lives in Forest, Mississippi. He is well-accepted and active in his community. He drives a car, plays golf, and spends time with the locals. In a recent historical book on autism, *In a Different Key: The Story of Autism*, and in their article in *The Atlantic*, John Donvan and Caren Zucker wrote in detail about Donald's early years as well as his current lifestyle. Visit www.DonaldT.com to read about him as well as watch a video.

Dr. Temple Grandin, age 68, continues to be a true inspiration not just to individuals on the autism spectrum and their families, but to the entire world. She is famous for her tireless efforts to promote the humane treatment of animals as well as for the insight and support she offers to families and professionals in the autism community. She is a celebrity in every sense of the word, and her books become instant must-read best sellers worldwide.

Dr. Rimland's son, Mark, turned 60 last month (March 2016). As most of you know, Mark's autism inspired his father to dedicate nearly 50 years of his life to autism, as a researcher and parent advocate. Mark lives with his mother and younger brother, attends an adult school for individuals with developmental disabilities, and continues his passion for creating art (watercolors, acrylic, and mosaics). Mark can ride the bus on his own and has many friends in his neighborhood.

The Ever-Pioneering Parents

Parents of seniors on the autism spectrum are strategizing about how their sons and daughters will receive appropriate support services when they can no longer care for them. These are the parents from the generation who were blamed for causing their young child's autism. Although Dr. Rimland's work led to the end of parent blaming, these seniors today were at least 10 years of age when his seminal book, *Infantile Autism*, was published in 1964.

These same parents had to rally and pressure the government in the 1960s and early 1970s to provide public education for children with disabilities. Their efforts culminated in the passage of the Individuals with Disabilities Education Act. When their teenagers reached adulthood some 40+ years ago, these are the same parents who had to figure out ways to support them beyond their school years.

Tom Brokaw used the phrase "the greatest generation" to describe military personnel who returned to the U.S. after World War II and made a real difference in providing stability and depth to American society. Brokaw once described these soldiers as "... ordinary people whose lives were laced with the markings of greatness." The *greatest generation* also applies to these pioneering and rarely recognized parents who strove for optimal, not minimal, support and education for their children as well as for future children.

The Numbers

How many seniors are on the autism spectrum? At first, this appears to be a difficult question to answer, especially since the CDC's prevalence statistics focus primarily on children. However, one can easily estimate a prevalence range given past and current published incidence rates.

As many of you know, there is much debate about whether the relatively high prevalence rate of 1 in 68 reflects an actual increase in autism over the past 30 years or an "apparent" increase due simply to better awareness, resulting in more diagnoses of autism.

If one assumes that the prevalence rate of autism has increased in the past three decades, then the estimated prevalence rate before the 1980s was 1 in 2,000 children. The 2013 U.S. census reports 63 million people who are age 60 and older. This would amount to *31,500* seniors with autism in the U.S. Using a less conservative statistical approach, if one assumes that the prevalence rate of autism has always been 1 in 68, this would total to *926,500*. In either case, the main point is that there are tens of thousands or possibly even hundreds of thousands of people on the autism spectrum in their senior years. If one were to harbor an educated guess, there are approximately a half-million seniors on the autism spectrum in the U.S.

Planning for the Senior Years

The needs of seniors on the autism spectrum are different from the needs of those who are in young adulthood or middle age. One big difference is their living situation, which may present uncertainties. Many, if not most, adults on the autism spectrum live with their parents, and these parents may no longer be able to care for them in the not-so-distant future. These seniors on the spectrum will someday need to move into another living situation, such as with another family member, in a group home, or possibly living semi-independently or independently.

Tom Brokaw used the phrase "the greatest generation" to describe military personnel who returned to the U.S. after World War II and made a real difference in providing stability and depth to American society. Brokaw once described these soldiers as "... ordinary people whose lives were laced with the markings of greatness." The greatest generation also applies to these pioneering and rarely recognized parents who strived for optimal, and not minimal, support and education for their children as well as for future children.

It is important to point out that medical problems common in children and adults on the autism spectrum may likely continue or even become much worse in their senior years. That is, many of the medical co-morbidities associated with autism are common in the elderly population as a whole. These include gastrointestinal and immune issues, sleep problems, seizures, sensory sensitivities, and low bone density. These possible health-related challenges need to be understood and taken into account with regard to appropriate health care and residential placement.

Besides health-related issues, cognitive processes often decline in the senior years. Many children and adults on the autism spectrum already have difficulties in executive processing and memory. How will their cognitive abilities change in advancing years?

Over the past 40 years, a number of reports have been published related to neuropathologic observations in the postmortem brains of autistic adults, studied in com-

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Research Updates:

Mouse study: Korean red ginseng beneficial

Korean red ginseng reduces autistic-like behaviors in a mouse model of autism spectrum disorders (ASD), according to a new study.

Edson Gonzales and colleagues investigated the effects of this type of ginseng on male offspring of mice injected with valproic acid during pregnancy. These offspring exhibit symptoms similar to those seen in autism.

When the mice reached 21 days of age (equivalent to early school age in human children), the researchers began giving them daily oral doses of Korean red ginseng (100 or 200 mg/kg). Between days 28 and 38 (a stage similar to human puberty), they tested the social interaction, locomotor activity, repetitive behaviors, short-term spatial working memory, motor coordination, and seizure susceptibility of the mice.

The researchers report, "Remarkably, long-term Korean red ginseng treatment at both dosages normalized all the ASD-related behaviors in valproic acid-exposed mice, except motor coordination ability."

Gonzales and colleagues say their findings indicate that Korean red ginseng may be capable of reducing symptoms of autism even after early brain development is complete. They call for further studies to isolate the chemicals in the ginseng that are responsible for its apparent effects.

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"Supplementation of Korean red ginseng improves behavior deviations in animal models of autism," Edson Luck T. Gonzales, Jong-Hwa Jang, Darine Froy N. Mabunga, Ji-Woon Kim, Mee Jung Ko, Kyu Suk Cho, Geon Ho Bahn, Minha Hong, Jong Hoon Ryu, Hee Jin Kim, Jae Hoon Cheong, and Chan Young Shin, *Food & Nutrition Research*, February 1, 2016 (online). Address: Chan Young Shin, Department of Pharmacology, School of Medicine, Konkuk University, 1 Hwayang-Dong, Gwangjin-Gu, Seoul 143-701, Korea, chanyshin@kku.ac.kr.

Iodine deficiency may be a factor in autism

Iodine deficiency may play a role in autism spectrum disorders (ASD), a new study suggests.

Anna Blażewicz and colleagues tested the urinary iodine levels and thyroid hormone levels of 40 boys with ASD ranging in age from 2 to 17 years, comparing the children to 40 neurotypical boys. They also administered the Child Autism Rating Scale (CARS) to the children with ASD.

The researchers report, "Nineteen out of 40 children with ASD had mild to moderate iodine deficiency." Levels of iodine in the ASD group were significantly lower than levels in the control group. The thyroid hormone levels of children with ASD were within normal reference ranges, but when the researchers controlled for a number of variables they determined that children with autism had significantly lower levels of fT3 and fT4 and higher levels of TSH.

The researchers say, "Concentration of iodine in urine was negatively associated with clinician's general impression for children between 11 and 17 years. Emotional response, adaptation to environmental change, near receptor responsiveness [taste and smell], verbal communication, activity level, and intellectual functioning are more associated with urinary iodine than other symptoms listed in CARS."

The researchers conclude, "The severity of certain symptoms in autism is associated with iodine status in maturing boys. Thyroid hormones were within normal reference ranges in both groups while urinary iodine was significantly lower in autistic boys suggesting that further studies into the nonhormonal role of iodine in autism are required."

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"Iodine in autism spectrum disorders," Anna Blażewicz, Agata Makarewicz, Izabela Korona-Glowniak, Wojciech Dolliver, and Ryszard Kocjan, *Journal of Trace Elements in Medicine and Biology*, Vol. 34, March 2016, 32-37. Address: Anna Blażewicz, Medical University of Lublin, Chodźki 4A, 20-093 Lublin, Poland, anna.blazewicz@umlub.pl.

Children of mothers with PCOS may be at increased risk for ASD

Children of mothers with polycystic ovarian syndrome (PCOS) may be at elevated risk for autism spectrum disorders (ASD), according to a recent study.

PCOS affects 5 to 15% of women of child-bearing age. Women with PCOS over-produce androgens (such as testosterone) that influence the development of male characteristics.

Kyriaki Kosidou and colleagues conducted a matched case-control study of more than 23,000 individuals with ASD and more than 208,000 controls matched by birth month and year, sex, and region of birth. The researchers report, "Maternal PCOS increased the odds of ASD in the offspring by 59%, after adjustment for confounders." Children of mothers with both PCOS and obesity (which also raises androgen levels) had an even greater risk of being diagnosed with ASD.

The researchers suggest that elevated androgens during pregnancy could affect the developing brain and nervous system of a fetus. A number of studies have suggested a link between autism and elevated androgen exposure in utero.

Senior study author Renee Gardner comments, "It is too early to make specific recommendations to clinicians in terms of care for pregnant women with PCOS, though increased awareness of this relationship might facilitate earlier detection of ASD in children whose mothers have been diagnosed with PCOS."

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"Maternal polycystic ovary syndrome and the risk of autism spectrum disorders in the offspring: a population-based nationwide study in Sweden," K. Kosidou, C. Dalman, L. Widman, S. Arver, B. K. Lee, C. Magnusson, and R. M. Gardner, *Molecular Psychiatry*, December 8, 2015 (epub prior to print publication). Address: Renee Gardner, Renee.Gardner@ki.se.

ADHD drugs may harm children's bones

Many individuals with autism take medications for attention deficit hyperactivity disorder (ADHD), and a new study cautions that these drugs may impact bone health.

In a sample of more than 5,300 pediatric patients, Jessica Rivera and colleagues compared those taking ADHD medications with those not taking the drugs. They found that children taking ADHD medications had lower bone mineral density in the femur, femoral neck, and lumbar spine. Approximately 25% of children on medication met criteria for osteopenia (lower than normal peak bone density), a number significantly higher than in the controls.

The researchers note that these drugs can cause stomach upsets and appetite loss, possibly leading to a lower intake of calcium. In addition, they say, the drugs may affect bone density because they alter the sympathetic nervous system, which plays an important role in bone regeneration.

Rivera and colleagues say that because most skeletal growth occurs by 18 to 20 years of age, doctors should consider nutritional counseling and other bone-protecting interventions for children taking ADHD medications.

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"ADHD medications associated with diminished bone health in kids," news release, American Academy of Orthopaedic Surgeons (AAOS). Rivera and colleagues presented their findings at the March 2016 annual meeting of AAOS.

Research Updates:

Brain anomaly may be marker for autism

French researchers say a specific "misfold" in the brain may be a marker for autism.

In their study, Lucile Brun and colleagues measured the depth of geometric markers called *sulcal pits*. A sulcal pit is the deepest point of each sulcus (groove) in the cerebral cortex. All of the folds on the brain's surface develop from sulcal pits.

Using MRI, the researchers examined the sulcal pits of 102 boys between the ages of 2 and 10 years. The group included 59 children with autism, 21 children with pervasive developmental disorder not otherwise specified (PD-NOS), and 22 neurotypical children.

Analysis showed that in Broca's area, a region involved in language and communication, the maximum depth of a sulcus was reduced in children with autism compared to the other two groups. However, the researchers found that counterintuitively, in individuals with autism, deeper sulcal pits in this region correlated with greater impairment in language skills.

The researchers say their findings indicate abnormal early development in this specific region and suggest that the anomaly they detected may be a useful tool in diagnosing autism.

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"Localized misfolding within Broca's area as a distinctive feature of autistic disorder," Lucile Brun, Guillaume Auzias, Marine Viellard, Nathalie Villeneuve, Nadine Girard, François Poinso, David Da Fonseca, and Christine Deruelle, *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, January 12, 2016 (online). Address: Christine Deruelle, christine.deruelle@univ-amu.fr.

—and—

"Is autism hiding in a fold of the brain?," news release, CNRS, January 13, 2016.

Maternal fish intake above U.S. recommended level may be beneficial

While pregnant women are cautioned against eating large amounts of fish because of its mercury content, a new study indicates that a maternal diet moderately high in fish can have beneficial effects on children's neuropsychological development and may help protect against autism.

Jordi Julvez and colleagues analyzed the diets of pregnant women participating in a Spanish study and evaluated 1,892 of their children at the age of 14 months and 1,589 at five years of age. Overall, the researchers report, consumption of seafood above the 340 grams per week recommended by U.S. guidelines was associated with improvements in children's neuropsychological scores.

They add, "As a new finding, a consistent reduction in autism-spectrum traits was also observed with total, lean, and large fatty fish consumption. These associations generally remained positive above the level recommended by the current U.S. guidelines."

The researchers conclude, "The present results suggest no adverse associations of high seafood consumption in pregnancy with offspring neurodevelopment. Moderate consumption of small and large fatty fish and lean fish during pregnancy is associated with moderate improvements in child neuropsychological development, including cognitive functions and autism-spectrum traits." However, they note that "a slight dilution of the association at the highest intake levels may be indicative of a weak counterbalancing association due to the potential harm of related contaminants."

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"Maternal consumption of seafood in pregnancy and child neuropsychological development: A longitudinal study based on a population with high consumption levels," Jordi Julvez, Michelle Méndez, Silvia Fernandez-Barres, Dora Romaguera, Jesus Vioque, Sabrina Llop, Jesus Ibarluzea, Monica Guxens, Claudia Avella-Garcia, Adonina Tardón, Isolina Riaño, Ainara Andiarena, Oliver Robinson, Victoria Arija, Mikel Esnaola, Ferran Ballester, and Jordi Sunyer, *American Journal of Epidemiology*, Vol. 183, No. 3, January 2016, 169-82 (online). Address: Jordi Julvez, ISGlobal, Center for Research in Environmental Epidemiology (CREAL), Barcelona Biomedical Research Park, C. Doctor Alguader 8, 08003 Barcelona, Spain, jjulvez@creal.cat.

Large numbers of kids with ASD wander

More than 26% of children with special needs wander away from adult supervision each year, according to a new study, and children with autism spectrum disorders (ASD) are at highest risk.

Bridget Kiely and colleagues used data from a 2011 Centers for Disease Control and Prevention survey of caregivers of more than 4,000 children between the ages of 6 and 17 years with special needs. They divided the children into three groups: children with ASD only, children with intellectual disability (ID) or developmental delay (DD) only, and children with both ASD and ID or DD.

The researchers found that children with autism, with or without ID or DD, were more likely to wander than children without ASD. Children 11 years of age or younger were at highest risk.

They also found that regardless of diagnosis, children who wandered were more likely to be unaware of danger, to have difficulty differentiating between strangers and familiar people, to show sudden mood swings and become angry quickly, to overreact, to get lost easily, and to panic in response to new situations.

"The kids who are most likely to wander are the kids who are least likely to respond appropriately to police or rescue personnel, potentially further jeopardizing their safety," says study coauthor Andrew Adesman. "First responders need to recognize that children or young adults with an autism spectrum disorder may overreact to some well-intentioned interventions and may be unresponsive to simple commands or questions."

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"Prevalence and correlates of elopement in a nationally representative sample of children with developmental disabilities in the United States," Bridget Kiely, Talia R. Migdal, Sujit Vettam, and Andrew Adesman, *PLOS ONE*, February 4, 2016 (online). Address: Andrew Adesman, AAdesman@northwell.edu.

—and—

"Cohen Children's Medical Center study: Children on autism spectrum more likely to wander, disappear," news release, February 4, 2016.

Asthma med risk studied

Prenatal exposure to asthma medications may increase the risk of autism, a new study suggests.

Nicole Gidaya and colleagues collected data on 5,200 individuals with autism spectrum disorders (ASD) and 52,000 controls in a case-control study using Denmark's health and population registers. The researchers report that among children exposed prenatally to β-2-adrenergic receptor agonist drugs, the risk for ASD was elevated at all time points, including preconception (odds risk, 1.3) and the first, second, and third trimesters (odds risks 1.3, 1.5, and 1.4, respectively).

However, Gidaya notes, "During an asthma exacerbation in pregnancy, the prenatal maternal stress response may be elevated, which would be harmful during a time when the fetal limbic system is considered to be the most vulnerable to such a stress response, especially before 32 weeks of gestation." Thus, she says, the risks of asthma medications need to be weighed against their benefits.

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"In utero exposure to β-2-adrenergic receptor agonist drugs and risk for autism spectrum disorders," Nicole B. Gidaya, Brian K. Lee, Igor Burstyn, Yvonne Michael, Craig J. Newschaffer, and Erik L. Mortensen, *Pediatrics*, February 2016 (online). Address: Nicole Gidaya, Drexel University School of Public Health, Philadelphia, Pennsylvania, ngidaya@gmail.com.

—and—

Prenatal exposure to asthma drugs may boost autism risk," Liam Davenport, *Medscape Medical News*, January 19, 2016.

Aging in autism: A call to action

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parison to age and sex-matched controls. To date, there has been very little focus on the aging brain in autism or potential correlations with disorders such as depression, anxiety, or dementia. Whether this is due to lack of clinical data available at the time of death, the small numbers of brains available in individuals with ASD over the age of 60 years, or the fact that neuroanatomic research related to autism has been more directed to trying to understand underlying neurobiological mechanisms is uncertain. Of potential interest is the fact that there have been a few recent publications that have hypothesized that there may be some neuroprotective factors at work in the autistic brain that may reduce the probability of the autistic individual developing some of the common age-related disorders as they age. These suggestions would be consistent with the general finding that testosterone levels, which are considered high in many individuals on the spectrum, may provide some form of protection against neurological problems associated with aging.

New Online Autism Senior Survey

We believe it is urgent for us to better understand the characteristics and needs of seniors on the autism spectrum. We recently began a research project to learn about various issues associated with aging in autism. A survey was recently posted online that includes questions on medical problems, sensory challenges, and behavioral issues as well as various aspects of living situation and lifestyle (e.g., recreation, daily living, and emotions).

If you are on the autism spectrum and are 50 years of age or older, we would appreciate your completing the online survey located at www.ASDSeniorSurvey.com. We also encourage family members who have a son or daughter or sibling on the autism spectrum to fill out the survey.

We would also appreciate donations to help support and expand our efforts to understand in more depth the medical issues associated with autism and aging. Donors who contribute $100 or more will receive an autographed gift copy of the book, *The Secret Night World of Cats*, which was illustrated by Mark Rimland and written by Helen Landalf, Mark's sister.

Moving?
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BP medication may improve conversational skills in autism

A medication commonly used to treat high blood pressure may improve the conversational skills of individuals with autism, a new study suggests.

The drug, propranolol, is a beta blocker. In addition to lowering blood pressure, it is often prescribed to treat anxiety, stage fright, and post-traumatic stress disorder. While the drug is considered relatively safe for short-term use, long-term use can result in side effects ranging from gastrointestinal problems to slow heartbeat and fainting.

Years ago, a study reported that propranolol could improve the language and social skills of individuals with autism. In the new placebo-controlled study, Rachel Zamzow and colleagues analyzed the effects of propranolol on the conversational skills of 20 participants with autism recruited from a treatment center.

The researchers gave participants either 40 milligrams of propranolol or a placebo. An hour later, they conducted a structured conversation with the participants, measuring six social skills needed to converse well: staying on topic, sharing information, reciprocity (shared conversation), transitions or interruptions, nonverbal communication, and eye contact. The researchers also measured participants' autonomic activity and anxiety levels.

The researchers report that propranolol improved performance in the areas of reciprocity and nonverbal communication. The effect was not associated with participants' autonomic activity or anxiety level. The researchers now plan to study the drug in a large clinical trial to determine the effects of regular doses.

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"Effects of propranolol on conversational reciprocity in autism spectrum disorder: a pilot, double-blind, single-dose psychopharmacological challenge study," Rachel M. Zamzow, Bradley J. Ferguson, Janine P. Stichter, Eric C. Porges, Alexandra S. Ragsdale, Morgan L. Lewis, and David Q. Beversdorf, *Psychopharmacology*, January 14, 2016 (online). Address: David Beversdorf, beversdorfd@health.missouri.edu.

—and—

"Blood pressure medicine may improve conversational skills of individuals with autism," news release, University of Missouri-Columbia, February 1, 2016.

High rate of Asperger syndrome seen in gender dysphoria

Young people with gender dysphoria have an elevated rate of Asperger syndrome, according to a new study. Individuals with gender dysphoria feel distress because there is a mismatch between their physical gender and their perceived gender.

Daniel Shumer and colleagues conducted a retrospective review of patient chart data from 39 consecutive patients between 8 and 20 years of age seen at a gender clinic. Of this group, 22 were biologically male and 17 were biologically female.

The researchers report, "Overall, 23.1% of patients (9 of 39) presenting with gender dysphoria had possible, likely, or very likely Asperger syndrome as measured by the Asperger Syndrome Diagnostic Scale (ASDS)." They note, however, that the ASDS is not validated as an ASD diagnostic tool in the absence of other diagnostic information, and that some answers that elevate scores on the test (for instance, "appears to be aware that he or she is different from others") could also pertain to gender dysphoria.

However, the researchers say their findings "are consistent with growing evidence supporting increased prevalence of ASD [autism spectrum disorders] in gender dysphoric children." For example, they note that a Dutch study reported a 7.8% prevalence of ASD in patients evaluated using a standardized diagnostic test (the Diagnostic Interview for Social and Communication Disorders) at a gender dysphoria clinic. In addition, they note that children with ASD evaluated at a U.S. neuropsychology clinic "were 7.59 times more likely than non-referred children to have gender variance as measured by the parent-reported Child Behavior Checklist."

The researchers say, "Our data support inclusion of ASD screening as part of any comprehensive gender assessment, especially as diagnosis of ASD has implications for management of gender dysphoria. For example, a patient with ASD and gender dysphoria may require specialized psychosocial interventions, focused on navigating unique social challenges encountered during hormonal and social transition from the natal sex to the affirmed gender."

The researchers say the cause of the association between Asperger syndrome and gender dysphoria is unknown. However, they note that genetic factors and differences in exposure to androgens (hormones that influence the development of male characteristics) have been implicated in both autism spectrum disorders and gender dysphoria.

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"Evaluation of Asperger syndrome in youth presenting to a gender dysphoria clinic," Daniel E. Shumer, Sari L. Reisner, Laura Edwards-Leeper, and Amy Tishelman, *LGBT Health*, January 2016 (online). Address: Daniel Shumer, University of Michigan Health System, Division of Pediatric Endocrinology, Medical Professional Building, Room D1205, 1500 E. Medical Center Drive, Ann Arbor, MI 48109, dshumer@med.umich.edu.

—and—

"Youths with gender dysphoria have higher rates of Asperger syndrome," news release, Mary Ann Liebert, Inc., January 13, 2016.

Children with ASD may be impaired in smelling odors

Children with autism spectrum disorders (ASD) are impaired at detecting odors, a new study indicates.

Hirokazu Kumazaki and colleagues measured the odor-detecting ability of 23 children with ASD and 20 neurotypical children. All of the children were between eight and 16 years of age. The researchers used a pulse ejection system, which they say resolves problems associated with other techniques.

The researchers exposed the children to two scents: isoamyl acetate (which smells like banana) and allyl caproate (which smells like pineapple). They showed the children three boxes on a touch screen, telling them to touch the boxes and determine which one emitted an odor. When the children touched a particular box in each trial, an odor was emitted.

The researchers exposed the children to stronger odors first, decreasing the strength of the odors until the children successfully completed all trials or failed to detect an odor. They report, "Children with ASD were insensitive to both isoamyl acetate and allyl caproate compared to children with typical development."

The researchers say that the effects of olfactory disturbances are pervasive. "For instance," they say, "odor has been shown to have influence on mood as well as autonomic, endocrine, and immune functions. Odors have also been shown to play an important role in inducing emotional reactions, imitating the actions of others, and regulating social interactions." In addition, they note, olfactory disturbances may contribute to the high rates of food selectivity in autism.

Thus, the researchers say, "insensitivity to some odors might have a tremendous impact on children with ASD" and may explain earlier research findings indicating that an abnormal response to smell is the strongest predictor of social impairment in children with ASD.

The findings of this research are also consistent with an earlier study (see ARRI 2015, Vol. 3) showing that children with ASD did not adjust their sniffing in a normal way when smelling pleasant or unpleasant odors. In that study, longer sniff durations for unpleasant versus pleasant odors correlated with greater social impairments.

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"Assessment of olfactory detection thresholds in children with autism spectrum disorders using a pulse ejection system," Hirokazu Kumazaki, Taro Muramatsu, Takashi X. Fujisawa, Masutomo Miyao, Eri Matsuura, Ken-ichi Okada, Hirotaka Kosaka, Akemi Tomoda, and Masaru Mimura, *Molecular Autism*, January 2016 (online). Address: Hirokazu Kumazaki, Research Center for Child Mental Development, University of Fukui, 23-3, Matsuokashimoaizuki, Eiheiji-cho, Yoshida-gun, Fukui 910-1193m Japan, kumazaki@tiara.ocn.ne.jp.

Shank3-related autism reversed in mouse model

(continued from page 1)

on later in life by adding tamoxifen to the animals' diet. Mice with the inactive gene exhibit compulsive behavior, motor abnormalities, and anxiety, and they avoid other mice.

Reactivating the gene in young adult mice eliminated their repetitive behavior and social avoidance but did not reverse their anxiety or motor symptoms. When the researchers reactivated the gene earlier, the mice's anxiety and motor coordination also improved. The researchers also found that the density of dendritic spines, which help to transmit synaptic signals, markedly increased in the striatum of treated mice.

"This suggests," study coauthor Guoping Feng says, "that even in the adult brain we have profound plasticity to some degree. There is more and more evidence showing that some of the defects are indeed reversible, giving hope that we can develop treatment for autistic patients in the future."

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"Adult restoration of Shank3 expression rescues selective autistic-like phenotypes," Yuan Mei, Patricia Monteiro, Yang Zhou, Jin-Ah Kim, Xian Gao, Zhanyan Fu, and Guoping Feng, *Nature*, February 17, 2016 (epub prior to print publication). Address: Guoping Feng, Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts 02142.

—and—

"Neuroscientists reverse autism symptoms," Anne Trafton, *MIT News*, February 17, 2016.

New finding complicates "extreme male brain" theory

Researchers reporting on a new twin study say their findings add "an intriguing complication" to the extreme male brain hypothesis of autism spectrum disorders (ASD). This hypothesis posits that high levels of testosterone in the womb are associated with higher levels of autistic and attention deficit hyperactivity disorder (ADHD) traits in children.

In the new study, Jonna Maria Eriksson and colleagues analyzed data gathered from parents of more than 16,000 fraternal twins using the Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC). "Assuming that having a male co-twin increases the prenatal exposure to testosterone," they say, "the prenatal androgenization theory of autism would predict a higher rate of autistic traits in females with a male co-twin." The same should also hold true, they say, for ADHD.

"Instead," they say, "the opposite result was found, that girls with a female co-twin were reported to have more ADHD and autistic traits than girls with a male co-twin. It was also significantly more common for boys and girls with a female co-twin to reach the lower cut-off for ADHD than for those with a male co-twin." The latter pattern also was seen for ASD, but did not reach statistical significance.

The researchers say their findings neither support nor refute the extreme male brain hypothesis, noting that a number of complex factors could account for their unexpected findings.

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"Effect of co-twin gender on neurodevelopmental symptoms: a twin register study," Jonna Maria Eriksson, Sebastian Lundström, Paul Lichtenstein, Susanne Bejerot, and Elias Eriksson, *Molecular Autism*, January 19, 2016 (online). Address: Jonna Maria Eriksson, jonna.eriksson@gmail.com.

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Stephen M. Edelson, Ph.D., Director.
The Autism Research Institute is a non-profit organization.
Editor: Stephen M. Edelson, Ph.D. • www.Autism.com

 ISSN No. 0893-8474