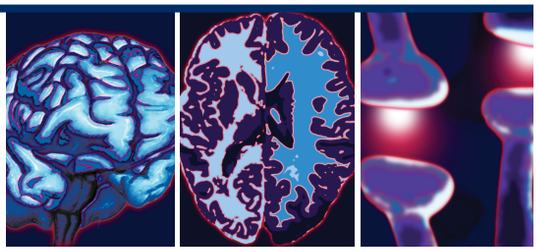


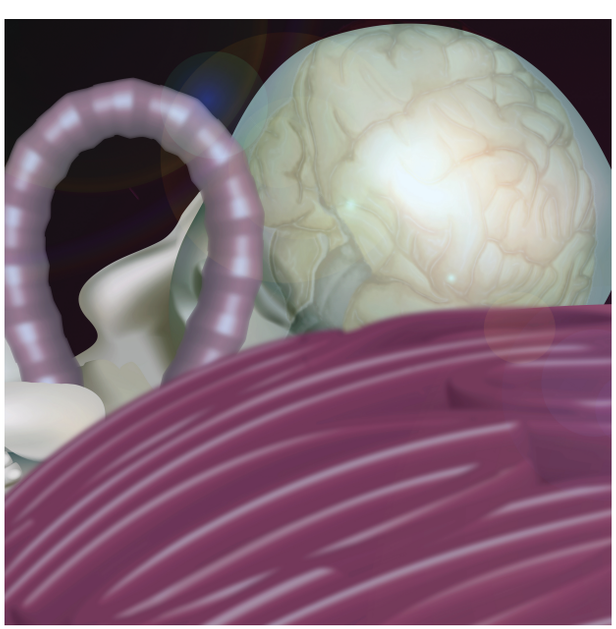
Autism diagnosis 'ahead of the game' with identification of placental abnormalities

Recent research, published in *Biological Psychiatry*, suggests that the risk of autism spectrum disorder could be predicted at birth by examining placental abnormalities.

Autism spectrum disorder (ASD) is a term encompassing a range of complex brain disorders; the CDC estimate that one in 88 children in the USA are identified as having ASD and prevalence estimates from the rest of the world average at approximately 1%.

Although diagnosis is reliable and valid when an infant reaches 2–3 years of age, most children are not diagnosed until 4 years or later. As the brain is highly responsive to treatment during the first year of life, strategies to diagnose ASD earlier are urgently needed. "Regrettably, couples without known genetic susceptibility must rely on identification of early signs or indicators that may not overtly manifest until the child's second or third year of life," explained senior author Harvey Kliman, research scientist in the Department of Obstetrics, Gynecology and Reproductive Sciences at the Yale School of Medicine (CT, USA).

In this study, Kliman and collaborators at the MIND Institute at the University of California, Davis (CA, USA) examined whether the presence of abnormal placental folds and cell growths, known as trophoblast inclusions (TIs), in the placenta could predict the infant's risk for ASD; the researchers describe gestation as a 'critical window' for neurodevelopmental vulnerability.



A total of 117 mothers who already had one or more previous biological children with ASD were selected from the MARBLES cohort as their newborns were considered to be at an elevated risk for neurodevelopmental compromise. Couples with a child with autism are nine-times more likely to have

"I hope that diagnosing the risk of developing autism by examining the placenta at birth will become routine..."

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another child with autism. The frequency of TIs in the placentas of these women was compared with controls. Control samples were obtained from 100 uncomplicated term pregnancies of women with one or more typically developing biological children.

Placentas from pregnancies considered 'at risk' had an eightfold increased chance of having two or more TIs compared with controls. The at-risk placentas had as many as 15 TIs, while none of the control placentas had more than two. The occurrence of two or more TIs predicted ASD risk with a sensitivity of 41% and a specificity of 92%. In addition, four or more TIs yielded a sensitivity of 19%, a specificity of 99.9% and conservatively predicted an infant with a 74% probability of being at risk for ASD.

These findings suggest that placental abnormalities may be a reliable predictor of ASD risk. "This is one of the largest studies to confirm this finding," said Geraldine Dawson, chief science officer for Autism Speaks, an advocacy and research group. These histological differences may point toward newborns who could benefit from early targeted interventions aimed at preventing or ameliorating behavioral symptoms and optimizing developmental outcomes.

Although the study only predicted risk of autism and not actual diagnoses of ASD, the test could help to spot at-risk children much earlier than is currently possible, which would put parents "ahead of the game," according to Kliman.

"I hope that diagnosing the risk of developing autism by examining the placenta at birth will become routine, and that the children who are shown to have increased numbers of TIs will have early interventions and an improved quality of life as a result of this test," concluded Kliman.

– Written by Sarah Freeston

Source: Walker CK, Anderson KW, Milano KM *et al.* Trophoblast inclusions are significantly increased in the placentas of children in families at risk for autism. *Biol. Psychiatry* doi:10.1016/j.biopsych.2013.03.006 (2013) (Epub ahead of print).

In utero exposure to valproate: is there an increased risk of autism spectrum disorder?

A study published in *JAMA* has raised concerns over a possible association between prenatal exposure to valproate, a commonly used treatment for epilepsy and other neuropsychological disorders, and risk of autism.

Previous studies have highlighted a potential association between antiepileptic drug exposure during pregnancy and an increased risk for congenital malformations or delayed cognitive development in the offspring; however, less is known about the risk of other serious neuropsychiatric disorders. Despite these previous findings, valproate is still commonly prescribed to women of childbearing age at a rate "that does not fully consider the ratio of benefits to risks," according to Kimford Meador and David Loring (Emory University, GA, USA), the authors of an accompanying editorial piece, who call for the use of the drug in these patients to be 'minimized', an effective alternative medication to be found, or the lowest possible dose of valproate used.

This population-based study included all children born in Denmark from 1996 to 2006 and followed them from birth until the soonest date out of the following: the day of autism diagnosis; death; emigration; or 31st December 2010. Average age at the end of follow-up was 8.84 years. National registers were used to identify children exposed to valproate during pregnancy and diagnosed with autism. Under the umbrella term 'autism spectrum disorders', the investigators included childhood autism, Asperger syndrome, atypical autism and other or unspecified pervasive developmental disorders. Data were analyzed and adjusted for confounders, such as maternal/paternal ages at conception, birth weight and gender.

Of the 655,615 children studied, 5437 were identified with autism spectrum disorder, of which 2067 were diagnosed with childhood autism. The estimated absolute risk after 14 years of follow-up was 1.53% for autism spectrum disorder and 0.48% for childhood autism. These figures can be compared with those of the 508 children who had been exposed to valproate: they had an absolute risk of 4.42 and 2.50%, respectively. If the cohort is restricted to the 6584 children born to women with epilepsy, the absolute

risk of autism spectrum disorder among 432 children exposed to valproate was 4.15%, and the absolute risk of childhood autism was 2.95% compared with 2.44 and 1.02%, respectively, among 6152 children not exposed to valproate.

The authors describe the increased risk of ASD in the offspring of mothers who took valproate during pregnancy as 'significant', even after adjusting for maternal epilepsy. The authors emphasize that even a moderate increase in ASD risk may have major health importance. However, as the absolute risk of ASD was less than 5%, the authors also caution that clinicians should take care when counseling women about taking valproate during pregnancy. The authors conclude that these findings should be balanced against the treatment benefits for women of childbearing potential who require valproate for epilepsy control.

– Written by Sarah Freeston

Sources: Christensen J, Koops Grønborg T, Juul Sørensen M *et al*. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 309(16), 1696–1703 (2013); Meador KJ, Loring DW. Risks of *in utero* exposure to valproate. *JAMA* 309(16), 1730–1731 (2013).

Study calls for integration and elimination of prejudice to reduce mental illness stigma

An international study, led by researchers from Indiana University (IN, USA), reports that researchers and policy makers need to improve efforts to reduce cultural barriers and reduce the prejudice associated with neuropsychological disorders.

Although the investigators found widespread acceptance that mental illness stems from medical causes and can be effectively treated, a 'backbone' of prejudice was found to exist across the 16 countries included in the study, which represented a diverse range geographically, developmentally and politically, with at least one country from each inhabitable continent. "We had a sense that prejudice and discrimination exist everywhere but we did not know about how much that varied or whether there were common problems. This study focused on the latter – the shared issues of prejudice," explained Bernice Pescosolido, Professor of Sociology at Indiana University (IN, USA), in correspondence with *Neuropsychiatry*.

> "...for the first time, we can see if there are a set of issues that present problems, across many societies, for individuals with mental illness and their families..."

"Up until now, we have had very little idea of the global landscape of stigma. There have been some nationally representative studies but they did not use the same questions. So, for the first time, we can see if there are a set of issues that present problems, across many societies, for individuals with mental illness and their families," clarified Pescosolido.

Data were analyzed from the Indiana University-led Stigma in Global Context – Mental Health Study, which discussed customized vignettes with 19,508 participants, including portrayals of individuals suffering from depression, schizophrenia or, the control group, asthma. Knowledge and prejudice were measured with existing questions and scales, and the researchers employed exploratory data analysis to examine public responses to 43 items.

Across countries, levels of recognition of mental illness and acceptance of neurobiological contributions, as well as acceptance of treatment, were high. Indeed, Pescosolido explained, "On the positive side, individuals indicated that they understood that these problems are serious, that people can improve with treatment and that there are multiple sources of help."

Having said this, five core prejudice items were found to be consistently high. The stigma was found to be strongest toward individuals with schizophrenia. Even in countries with cultures deemed to be more accepting of mental illness, the 'backbone' of stigma was still found surrounding issues such as childcare, marriage and self-harm. Stigma is considered to be a significant obstacle to effective treatment. Patients can experience discrimination in employment, housing and medical care, all of which impact negatively on quality of life.

> "The stereotype of all individuals with mental illness being 'not able' is just wrong. No data support this..."

This stigma included beliefs that individuals with disorders, such as depression and schizophrenia, are unfavorable for close personal relationships and authoritative positions. "In every country over two-thirds of respondents, who were selected scientifically to provide a picture of the country as a whole, indicated that they were unwilling to have individuals described with schizophrenia or depression care for or teach their children or have them as in-laws. They reported individuals with mental illness to be unpredictable and be likely to hurt themselves," explained Pescosolido.

"The stereotype of all individuals with mental illness being 'not able' is just wrong. No data support this," said Pescosolido, who continued, "with the

prevalence of mental health problems being so high, no individuals or families will go untouched by these issues. They need to understand that recovery is not only possible but has been documented."

These data can be used to realign public health efforts to reduce stigma and to determine important issues for treatment providers to consider. The authors highlight the importance of prioritizing integration and inclusion to reduce cultural barriers.

> "...with the prevalence of mental health problems being so high, no individuals or families will go untouched by these issues."

Providers "have to actively ask about [these stereotypes] during treatment, undermine these prejudices for family and friends (as well as the person) and also prepare individuals for what they may face in the community," concluded Pescosolido.

– Written by Sarah Freeston

Source: Pescosolido BA, Medina TR, Martin JK, Long JS. The 'backbone' of stigma: identifying the global core of public prejudice associated with mental illness. *Am. J. Pub. Health* 103(5), 853–860 (2013).

About the News

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Clostridium bolteae vaccine could help control some symptoms of autism

In a recent study, researchers from the University of Guelph (ON, Canada) have generated a first-ever vaccine for gut bacteria common in autistic children. It is hoped that the vaccine will help control some symptoms of autism and has been developed using a carbohydrate-based vaccine against the gut bacteria *Clostridium bolteae*.

The rise in autism diagnosis has resulted in an almost sixfold increase in cases over the past two decades. The reasons for this have split opinion between scientists, with some experts pointing to environmental factors, while others have focused on the human gut. *C. bolteae* often shows up in higher numbers in the GI tracts of autistic children and is known to play a role in gastrointestinal disorders with more than 90% of children with autism disorders suffering from chronic, severe gastrointestinal symptoms. Furthermore, some researchers believe toxins and/or metabolites produced by gut bacteria, such as *C. bolteae*, may be associated with the symptoms and severity of autism, especially that of regressive autism.

The new vaccine targets conserved specific capsular polysaccharides on the *C. bolteae* surface. The vaccine was found to effectively raise *C. bolteae*-specific antibodies in rabbits, which can also potentially be used as a diagnostic marker for the rapid detection of *C. bolteae* in a clinical setting. Mario Monteiro from the University of Guelph describes the breakthrough, "This is the first vaccine designed to control constipation and diarrhea caused by *C. bolteae* and perhaps control autism-related symptoms associated with this microbe." Although most infections are handled by some antibiotics, a vaccine would improve current treatment.

It is likely that it will take many years for the vaccine to progress past the stages of preclinical and human trials; however, "this is a significant first step in the design of a multivalent vaccine against several autism-related gut bacteria", comments Monteiro. The researchers in this group have also studied sugar-based vaccines for two other gastric pathogens: *Campylobacter jejuni*, the cause of travellers' diarrhea; and *Clostridium difficile*, the cause of antibiotic-associated diarrhea, the latter of which was recently reviewed in the *Expert Review of Vaccines* April issue.

– Written by Jenaid Rees

Sources: Monteiro MA, Ma Z, Bertolo L *et al.* Carbohydrate-based *Clostridium difficile* vaccines. *Expert Rev. Vaccines* 12(4), 421–431 (2013); Pequegnat B, Sagermann M, Valliani M *et al.* A vaccine and diagnostic target for *Clostridium bolteae*, an autism-associated bacterium. *Vaccine* doi:10.1016/j.vaccine.2013.04.018 (2013) (Epub ahead of print).