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Headline

Unveiling risk factors of autism: Current evidence

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Over the past decades, rising prevalence of autism has been noted worldwide[1]. The pooled prevalence of autism spectrum conditions was 26.6 per 10,000 in China, Hong Kong and Taiwan[2]. While the etiology is still obscure[3]; mothers across different ethnic groups believed environmental and genetic factors caused autism[4]. Plausible risk factors have been summarized in this article.

Genetic factors

Association between vitamin D insufficiency and autism sheds light on the **potential role of vitamin D receptor genes**[4-6]. Zhang and colleagues inspected the relationship between polymorphisms in vitamin D receptor genes and childhood autism in a Chinese population (201 children with autism; 200 healthy controls)[4]. The CT genotype (p = 0.0351) and C allele (p = 0.0416) of *TaqI* (rs731276) were significantly related to raised risks of childhood autism, although none of the polymorphisms were correlated with the severity of disease status[4].

Maternal folate status

Folate, a methyl donor, can influence DHA methylation pattern during peri-conceptional period that may lead to epigenetic dysregulation linking to alterations in brain functions and then autism development[7,8]. DeSoto and Hitlan investigated data from a large-scale project and found that autistic children were more likely to have mothers who took folic acid supplements during pregnancy[9].

A prospective cohort in Spain suggested that children born to women taking folic acid supplement more than 5,000 mcg daily during pregnancy had a significantly lower mean psychomotor scale score (difference, -4.35 points; 95% CI, -8.34 to -0.36) than those whose mothers took a lower dose of folic acid[10]. 5,000 mcg per day folic acid supplementation was also linked to a higher risk of delayed psychomotor development (psychomotor scale score < 85)[10].

Nevertheless, a meta-analysis, analyzing 12 articles with 4,514 autism cases, concluded that supplementation with folic acid during pregnancy could reduce the risk of autism (RR = 0.77, 95% CI = 0.641 – 0.928) as compared with mothers without supplement[11]. Although the collective evidence of folic acid supplementation remains inconclusive, following the recommended intake helps fulfil the nutritional need of women with low risk of neural tube defects, for example, **the Chinese Dietary Reference Intake of folic acid for pregnant women aged 18 to 49 years is 600 mcg daily**[12].

Gut-brain axis

Aberrant neurodevelopmental processes like network pruning that influence brain development may be another explanation for autism since autistic children exhibited abnormalities in brain connectivity measured by electroencephalography[13,14]. Concurrence of gastrointestinal issues and higher level of

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affective problems in children with autism implicated the role of gut-brain axis[15].

Autistic symptoms in children were correlated with a less diverse gut microbiome, for example, less carbohydrate fermenting bacteria of the genera *Prevotlla*, *Coprococcus* and the unclassified *Veillonellaceae* was measured in autism fecal samples[16,17]. The enhanced intestinal permeability in autistic patients may allow potentially neuroactive microbial metabolites to across the intestinal membrane, contributing to the development of autism[18,19].

Oral vancomycin intervention exerted temporary improvements in behavior and communication in children with regressive-onset autism[20]. Furthermore, a case study of a 12-year-old boy with autism and severe cognitive disability suggested the benefits of probiotic treatment[21]. **Ingestion of a multi-strain mixture of 10 probiotics for 4 weeks improved core autism symptoms and the score of Social Affect domain of Autism Diagnostic Observation Schedule changed from 20 to 17**[21]. Appropriate manipulation of gut microbes may be an innovative therapeutic option for autism.

Environmental toxins

Heavy metal exposure demonstrated a close association with child behavioral development. Even within blood lead levels from 0.19 to 3.25 mcg/dL, levels far below the reference level for children (> 5 mcg/dL), **increasing lead levels resulted in higher levels of hostile distrust and oppositional defiant behaviors**[22]. Those children had difficulties in communications and were more dissatisfied and uncertain about their emotions[22]. Autistic children showed significantly higher levels of mercury and arsenic ($p < 0.001$) whereas no significant difference was recorded for lead[23]. In addition, more autistic behaviors in children (5 years) were associated with blood mercury levels during late pregnancy as well as early childhood[24].

Pregnancy complications

Late-preterm infants (LPIs), born between 34 + 0 and 36 + 6 gestational weeks, showed higher rates of neurodevelopmental disorders compared with the general population and 13.2% LPIs (9 out of 68) were diagnosed with autism[25]. Maternal hypertension, a late preterm birth risk factor, was demonstrated to associate with a higher risk of autism as well as attention-deficit/hyperactivity disorder (ADHD)[26,27]. Having an ideal pre-pregnancy weight is a key step to optimize pregnancy outcome. A newly published study further indicated that **women with pre-pregnancy obesity (BMI ≥ 30) were more likely to have children with high scores (≥ 26) on the Autism-Spectrum Quotient** ($p = 0.01$)[28].

Parents make a difference!

⇒ For all infants, **higher level of maternal responsiveness was related to higher level of social smiling** - smiling with eye contact directed towards a social partner[29]

⇒ Higher maternal directiveness was noted in infants at high familial risk for autism and those infants showed better growth in social smiling versus those at low risk[29]

Parenting style contributes to the development of social engagement in infants

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Latest Science

Cow's milk protein allergy - What's new in research?

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Pathophysiology

Allergic reactions to cow's milk in infants may either persist throughout childhood, or some may gradually become tolerant when they grow up[1]. A Sweden cohort study of 2,985 children found that early life milk-related symptoms were common, affecting 20% of the cohort and most commonly reported at ages 2 to 4 years[1]. When followed to 16 years old, this figure fell to 2% with persistent symptoms reported, **indicating that most early life cases were in fact transient**[1].

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Risk reduction

Human milk oligosaccharides (HMOs) can help to shape the infant's gut microbiota and may potentially impact on the maturation of the intestinal mucosal immune system[2]. A study has explored the role of HMOs in allergy prevention, which found **low concentrations of Lacto-N-fucopentaose (LNFP) III (a type of HMO)** (< 60 μM) **in human milk were associated with a higher risk of cow's milk protein allergy** within the first 18 months of life in infants at high risk of food allergies (OR 6.7, 95% CI 2.0-22)[2]. On the other hand, a review paper by Miliku *et al.* (2018) examined the associations of 19 HMOs with food sensitization at one year of age, and did not observe associations of any individual HMOs with food sensitization. However, **overall HMO profiles differed significantly in the milk consumed by sensitized and non-sensitised infants**[3].

Treatment

Oral immunotherapy (OIT) is a recognized treatment for severe and long-term cow's milk protein allergy, including an induction phase with gradual dosing of cow's milk to a target level, followed by a maintenance phase where patients keep a steady daily intake to ensure continued desensitisation[4]. A prospective study assessed the long-term efficacy and safety of the maintenance phase of cow's milk OIT in children aged 2 to 18 years (n = 42), with a maintenance dosage of 200 mL cow's milk daily over 3 years[4]. **Approximately 45% of the subjects developed mild to severe allergic reactions during the maintenance phase, where a history of anaphylaxis was a significant risk factor** (80% in subjects with previous history in comparison to 26% in subjects who didn't, OR 11.382, p < 0.001)[4]. **Adherence was also important, as clinical tolerance of cow's milk seems to be quickly lost after suspension**[4]

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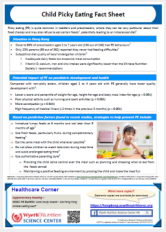
Latest WNSC HK Info Card



Child Picky Eating Fact Sheet

A summary of the latest science and tips on preventing picky eating behaviour in children

Distribution of the Info Card by healthcare professionals is welcomed. Electronic copy is available on the WNSC HK website under "WNSC Publications" for download and reprint.

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Monthly Health Focus

World Diabetes Day

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World Diabetes day, officially marked on November 14th of each year, was enacted by the International Diabetes Federation (IDF) and the World Health Organization (WHO) in response to the growing concerns to the increasing health impact of diabetes[1,2]. **This Diabetes awareness campaign, with a global reach to over 1 billion people across more than 160 countries, is represented by a blue circle logo - an internationally recognized icon adopted by the United Nations** to symbolize the concerted efforts of the global community in response to this epidemic[2].

In Hong Kong, diabetes mellitus (DM) is currently the tenth leading cause of mortality, accounting for 492 registered deaths or 1.1% of all deceases in 2015[3]. **The prevalence of DM has more than doubled since the 1990s, and recent data shows it affects approximately 700,000 people, or around one in every ten people of the Hong Kong population**[4,5].

Of the three major types of diabetes (Type 1 diabetes, Type 2 diabetes, and gestational diabetes), Type 2 diabetes is the most common form of diabetes in Hong Kong, affecting over 90% of all DM cases[4,5]. For mothers-to-be, gestational diabetes (GDM) affects at least 20% of this subgroup locally[6]. Results from a recent study released by CUHK in 2017 indicates that **children born to mothers with GDM has a 3-fold increased risk of developing prediabetes or diabetes, and has a 50% higher rate of overweight and obesity**[6].

On a positive note, there are certainly things that we can do to help prevent diabetes. Of the various modifiable risk factors

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for DM, lifestyle-related factors such as nutrition play a significant role. Recent results from The Singapore Chinese Health Study suggest that **predefined dietary patterns were significantly associated with a 16% (for alternate Mediterranean diet) to 29% (for Dietary Approaches to Stop Hypertension diet) reduction in risk of developing Type 2 Diabetes** in an Asian population[7].

Making healthy food choices can be a part of our daily decisions to help promote good health. For practical tips on healthy eating, please check out our WNSC Healthy Eating Tips Cards:

https://hongkong.wyethnutritionsc.org/en/publications/healthy-eating-tips-card

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Featured News

A2 protein - What is it all about?

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β-casein (BC) protein exists in bovine milk as two variants, either A1 or A2 type depending on the cow's genetic makeup[1,2]. The two differ in a point mutation at the amino acid residue 67, leading to differences in their protein structures and thus proteolytic digestion products, **with A2 BC showing more resemblance to human milk protein in this digestive respect**[1,3,4].

β-casomorphin-7 (BCM7) is a peptide uniquely derived from the digestion of A1 BC, but not A2 BC or human milk protein[1,3,4]. It has a high affinity to opioid receptors in the nervous, endocrine and immune systems, and may also down-regulate glutathione expression and its associated antioxidant capacity in cells[1,5]. BCM7 is therefore potentially associated with various disease states including autism, cardiovascular disease, type 1 diabetes and schizophrenia[5].

The selective production of milk with just A2 BC is now possible with specific selection and genotyping of cows with both A2 alleles[2]. A randomized controlled trial found healthy adults consuming A2 milk (milk with A2 BC) did not show increased plasma BCM7 levels and they also had increased glutathione disulfide (GSH) production[1]. Similarly, **during simulated gastro-intestinal digestion (SGID) of an infant's stomach with a formula based on A2 milk, a much lower BCM7 level was detected** with 0.86 mcg/100 mL, compared to an average level of 2.09 mcg/100 mL for commercial formulas which contained a higher level of A1 BC ($p < 0.05$)[2].

BCM7 has also been implicated in the adverse gastrointestinal effects of drinking milk, possibly due to its morphine-like effects to slow gut motility[3,5]. A study by Sun *et al.* (2017) found post-dairy digestive discomfort symptoms in a lactose intolerant adult subject group were significantly exacerbated when milk with both BC types were consumed[3]. It was also associated with higher concentrations of BCM7, inflammatory biomarkers, as well as longer gastrointestinal transit times compared to baseline, while consumption of just A2 milk did not[3]. **These results indicate consumption of A1 BC disrupted the digestive process and may elucidate that symptoms of lactose intolerance can possibly stem from effects triggered by BCM7 released from A1 BC in milk**[3]. This is an interesting area to continue research into to further determine the clinical implications of A2 milk in both infant and adult health.

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