MICROBIAL ECOLOGY in Health and Disease

co-action PUBLISHING

THE MICROBIOME IN AUTISM SPECTRUM DISORDER

Introduction

Richard E. Frye[1,2] and John Slattery[1,2]

[1]Autism Research Program, Arkansas Children's Hospital Research Institute, Little Rock, AR, USA;
[2]Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Autism spectrum disorder (ASD) is a devastating neurodevelopmental disorder currently estimated to affect 1 in 68 individuals in the United States (1). The biological underpinnings of ASD are unclear at this time. Although research has concentrated on genetics (2), single gene defects and chromosomal abnormalities only account for a minority of ASD cases (3). An increasing number of research studies support evidence for underlying physiological disturbances, including mitochondrial dysfunction, immune dysregulation, and oxidative stress (2, 4, 5), which may be pathophysiological hallmarks of a very complex disease process that contribute, at least in part, to medical comorbidities associated with ASD as well as core and associated ASD symptoms. Furthermore, it is becoming clear that the internal environment of affected individuals as well as disturbances from the external environment (e.g. biome, diet, toxicants) play a significant role in the development of ASD, although the exact mechanisms behind these influences and how they contribute to a complex phenotypic expression of ASD is unclear at this time (2, 6). To this end, it is essential to have a broad consideration of factors that could cause and/or contribute to the development of ASD.

One interesting aspect of ASD, and perhaps a clue to the putative etiological factors at play, is the medical conditions associated with ASD. One of the most prevalent reported medical conditions is gastrointestinal (GI) disorders (7). Not only are GI symptoms very prevalent, but many parents report significant improvements with change in diet. Parallel to the increasing awareness of the GI system and diet in relation to ASD, the general scientific and medical communities have been recognizing that the trillions of microbes that inhabit the human digestive tract, the so-called enteric microbiome, may influence host physiology, including the immune system and metabolism (8, 9), and may play a major role in modulating normal brain development as well as directly modulating behavior (10–12). This has resulted in studies more closely investigating the possible involvement of the enteric microbiome in ASD (13, 14).

To accelerate the dissemination of knowledge, a worldwide collaboration between leaders in this field was held on Thursday, June 26, 2014 at the *1st International Symposium on the Microbiome in Health and Disease with a Special Focus on Autism* (www.microbiome-autism.com). The symposium included clinicians, research scientists, and parents of children with ASD (See Table 1).

Important highlights from the symposium are documented within seven manuscripts in this special issue of *Microbial Ecology in Health and Disease* along with this introduction and concluding remarks by Dr. Tore Midtvedt, the editor-in-chief of the journal.

Two papers provide interesting perspectives on the microbiome with respect to health and disease, particularly commenting on how the microbiome may have changed because of self-imposed societal changes in environmental exposures and diet. Drs Toh and Allen-Vercoe provide a nice introduction to the microbiome and the recent realization of its importance and then comment on common changes in medicine and lifestyles which may lead to a decrease in microbial diversity, potentially leading to chronic disease such as ASD (15). Drs Bilbo, Nevison, and Parker then point out how the microbial flora as well as the fauna have changed because of modern Western culture, possibly leading to a rise in immune dysregulation and autoimmune disease, particularly commenting on the 'Biome Depletion' theory of immune disease (16). They nicely point out the connections with ASD through immune abnormalities associated with ASD.

Three papers more directly address the relationship between the microbiome and ASD. A group of leaders in the microbiota changes association with ASD from Arizona State University provide an excellent summary of the research connecting ASD with GI disorders and changes in the enteric microbiome (13). They provide unique and original data supporting the notion that the Western diet has resulted in a shift in the microbiome composition. In another review article, leaders in the field of abnormalities in mitochondrial function and propionic acid in relation to ASD discuss the significance of mitochondrial disorders in ASD with respect to GI symptoms and how enteric bacteria may induce or

Citation: Microbial Ecology in Health & Disease 2015, **26**: 28168 - http://dx.doi.org/10.3402/mehd.v26.28168

Table 1. Presentation at the 1st *International Symposium on the Microbiome in Health and Disease with a Special Focus on Autism*

Time	Speaker	Presentation Title
8:00–8:15	Richard Frye, MD, PhD	Introduction to the Symposium
8:15–8:30	John Rodakis, BS	An Autistic Child's Response to Antibiotics: An N of One Case
8:30–9:30	Carl Cerneglia, PhD	Microbiome and the Environment
9:45–10:45	Emma Allen-Vercoe, PhD	The Human Gut Microbiota: Forgotten Organ, Important Ally
10:45–11:45	Tore Midtvedt, PhD	The Gut and the Brain: A Scandinavian way of Approaching Autism
11:45–12:45	William Parker, PhD	The (Potential) Role of Fauna and Flora Disruption in the Human Body as Constituents to the Development of Autism
1:30–2:30	Jim Adams, PhD and Rosa Krajmalnik-Brown, PhD	Gut Bacteria in Children with Autism
2:30–3:30	Derrick MacFabe, MD	Gut Bacterial Metabolites as Possible Environmental Triggers of Autism Spectrum Disorder
3:45–4:45	Richard Frye, MD, PhD	The Influence of Microbiome Metabolites on Mitochondrial Function in Children with Autism Spectrum Disorder
4:45–5:45	Susan Swedo, MD	PANDAS/PANS and the Microbiome

contribute to this association. A discussion of possible treatment approaches is outlined in light of the evidence reviewed (17). Lastly, a parent describes his journey to better understand the connection between the enteric microbiome and ASD after he observed a dramatic positive response to antibiotic treatment in his son with ASD (18). This latter paper emphasizes the importance and limitations of careful individual case observations.

Beyond the theoretical aspect of the connection between the microbiome and ASD, careful attention must be paid to the methods to studying this connection. This is extremely important for advancing the scientific and clinical evidence of this work. Two papers take on this point and outline the approaches and challenges ahead for this field. A group of well-known leaders discuss the use of large-cohort longitudinal studies to remove important sources of variation with examples from ongoing scientific studies, such as the American Gut Project, which are attempting to study the microbiome systematically (19). As an extension of the *1st International Symposium on the Microbiome in Health and Disease with a Special Focus on Autism*, a workshop aimed at outlining the challenges and approaches for conducting clinical trials focusing on systematically manipulating the enteric microbiome in individuals with ASD was held (20). This workshop included the symposium participants as well as other stakeholders and focused on better understanding the therapeutic potential of this research. The workshop produced important guidelines for consideration when conducting therapeutic trials in individuals with ASD. Together, these papers demonstrate the large-scale challenges that need to be overcome to better understand the human enteric microbiome and the challenges that revolve around possible ways to manipulate the enteric microbiome with the hope of improving health and combating disease.

References

1. Developmental Disabilities Monitoring Network Surveillance Year Principal I, Centers for Disease C, Prevention. Prevalence of autism spectrum disorder among children aged 8 years – autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveill Summ 2014; 63: 1–21.
2. Rossignol DA, Frye RE. A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures. Mol Psychiatry 2012; 17: 389–401.
3. Schaefer GB, Mendelsohn NJ, Professional P, Guidelines C. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med 2013; 15: 399–407.
4. Frye RE, James SJ. Metabolic pathology of autism in relation to redox metabolism. Biomark Med 2014; 8: 321–30.
5. Rossignol DA, Frye RE. Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. Front Physiol 2014; 5: 150.
6. Rossignol DA, Genuis SJ, Frye RE. Environmental toxicants and autism spectrum disorders: a systematic review. Transl Psychiatry 2014; 4: e360.
7. Chaidez V, Hansen RL, Hertz-Picciotto I. Gastrointestinal problems in children with autism, developmental delays or typical development. J Autism Dev Disord 2013; 44: 1117–27.
8. Holmes E, Li JV, Marchesi JR, Nicholson JK. Gut microbiota composition and activity in relation to host metabolic phenotype and disease risk. Cell Metab 2012; 16: 559–64.
9. Nicholson JK, Holmes E, Kinross J, Burcelin R, Gibson G, Jia W, et al. Host-gut microbiota metabolic interactions. Science 2012; 336: 1262–7.
10. Diaz Heijtz R, Wang S, Anuar F, Qian Y, Bjorkholm B, Samuelsson A, et al. Normal gut microbiota modulates brain development and behavior. Proc Natl Acad Sci USA 2011; 108: 3047–52.
11. Borre YE, Moloney RD, Clarke G, Dinan TG, Cryan JF. The impact of microbiota on brain and behavior: mechanisms & therapeutic potential. Adv Exp Med Biol 2014; 817: 373–403.
12. Borre YE, O'Keeffe GW, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota and neurodevelopmental windows:

implications for brain disorders. Trends Mol Med 2014; 20: 509–18.
13. Krajmalnik-Brown R, Lozupone C, Kang DW, Adams JB. Gut bacteria in children with autism spectrum disorders: challenges and promise of studying how a complex community influences a complex disease. Microb Ecol Health Dis 2015; 26: 26914, doi: http://dx.doi.org/10.3402/mehd.v26.26914
14. Williams BL, Hornig M, Buie T, Bauman ML, Cho Paik M, Wick I, et al. Impaired carbohydrate digestion and transport and mucosal dysbiosis in the intestines of children with autism and gastrointestinal disturbances. PLoS One 2011; 6: e24585.
15. Toh MC, Allen-Vercoe E. The human gut microbiota with reference to autism spectrum disorder: considering the whole as more than a sum of its parts. Microb Ecol Health Dis 2015; 26: 26309, doi: http://dx.doi.org/10.3402/mehd.v26.26309
16. Bilbo SD, Nevison CD, Parker W. A model for the induction of autism in the ecosystem of the human body: the anatomy of a modern pandemic? Microb Ecol Health Dis 2015; 26: 26253, doi: http://dx.doi.org/10.3402/mehd.v26.26253
17. Frye RE, Rose S, Slattery J, Macfabe D. Gastrointestinal dysfunction in autism spectrum disorder: The role of the mitochondria and the enteric microbiome. Microb Ecol Health Dis 2015; 26: 27458, doi: http://dx.doi.org/10.3402/mehd.v26.27458
18. Rodakis J. An n = 1 case report of a child with autism improving on antibiotics and a father's quest to understand what it may mean. Microb Ecol Health Dis 2015; 26: 26382, doi: http://dx.doi.org/10.3402/mehd.v26.26382
19. McDonald D, Hornig M, Lozupone C, Debelius J, Gilbert JA, Knight R. Towards large-cohort comparative studies to define the factors influencing the gut microbial community structure of ASD patients. Microb Ecol Health Dis 2015; 26: 26555, doi: http://dx.doi.org/10.3402/mehd.v26.26555
20. Frye RE, Slattery J, MacFabe DF, Allen-Vercoe E, Parker W, Rodakis J, et al. Approaches to studying and manipulating the enteric microbiome to improve autism symptoms. Microb Ecol Health Dis 2015; 26: 26878, doi: http://dx.doi.org/10.3402/mehd.v26.26878