

Food Intolerance and Autism

Received: August 30, 2020, Accepted: October 12, 2020, Published: October 19, 2020

Abstract

The purpose for research is inspiration from one child with autism in my family, from heteroanamnesis and symptoms, I decided to do the test-the first daughter of my sister with diagnosis autism, she had multi food intolerance, than with prof.Blyta we started with follow up panel (a big panel with more analysis of blood, urine, fecal, biochemistry also microbiology) but the first test was food intolerance for those patients. The connection between Autism and food intolerances is likely to lie in the higher prevalence of intestinal permeability that it seen in autistic patients. They have intestinal permeability, the largest protein undigested into the blood, from this process can develop food intolerance and food allergy. For food intolerance is responsible IgG or IgG4 and those antibodies reacted as adaptive immune system. The IgG antibodies then fix to the food proteins to form an immune complex in the blood stream. If the immune complex fixes to a tissue it will eventually lead to tissue damage from inflammation and specific symptoms which vary from person to person. Is the most important casein intolerance and gluten intolerance because from casein has a pathological mechanism of casomorphine formation aslo from gluten intolerance to gliadinomorphine ,these findings are specific for pathologies such as Autism delays in psychomotor, delays in speech, mood, anxiety, hyperactivity etc, but it is another of my research on gliadinomorphine and casomorphine with Autistic childrens.

Keywords: Autism; Food Intolerance; IgG4 Human Specific; Rapid-Blood Test

Introduction

The purpose of the research was inspired by a child with Autism in my family from hetero-anamnesis and clinical symptomatology and I decided to do the test initially my niece with the diagnosis of Autism, she had multi food intolerance, then with Prof.Blyta we started the follow Up panel (a big laboratory panel: Blood, Urine, Stool, in Biochemistry also Microbiology) but the first test was Food Intolerance for those patients.

Mechanism and connection between Food Intolerance and Autism

The connection between Autism and Food Intolerance is likely to be unreliable in the higher prevalence of intestinal permeability that it is seen in ASD patients, so they have intestinal permeability, the largest protein undigested into the blood (the cause is digestive enzyme deficit for undigested protein), from this process, it is possible to develop food intolerance and food allergy, but our research had in focus food intolerance in ASD patients. From causes of food intolerance (which are detailed later on), the responsible is IgG or subclasses of IgG4, these antibodies reacted as adaptive immune system.Mechanism the IgG4 antibodies then fix the food proteins to form an immune complex in the blood stream, if the immune complex fixes to a tissue it will eventually lead to tissue damage from inflammation and specific symptoms which vary from person to person. The most important are Casein and Gluten intolerance because from casein has a pathological mechanism of Casomorphine formation

also from Gluten to Gliadinomorphine formation findings from them are delays in speech, mood, delays in psychomotor, anxiety, hyperactivity etc (but these findings are another research for ASD).

Causes of Food Intolerance

Food is composed of protein, carbohydrate, fat, vitamins also various nutrients as well a number of natural chemicals as monosodium glutamate, such foods as tomatoes, soya sauce, mushrooms, in some cheese. Monosodium glutamate stimulates nerve endings, perhaps accounting for its function as a flavour enhancer when it is added to food.Vasoactive amines such as tyramine, serotonin and histamine are present naturally in pineapples, bananas, baked meat, vegetables, red wine, wood-matured, white wine, avocados, chocolate, citrus fruits and mature cheese. Other are Salycilates, such as some fruits and vegetables, toxines, irritants as caffeine, celiac disease, non celiac gluten intolerance and digestive enzyme deficiencies. The most important from all should be enzyme deficiencies such as Amylase, Lipase, Protease, Lactase, and Aldolase. Amylase is a digestive enzyme that acts on starch in food breaking it down into smaller carbohydrate molecules. Salivary Amylase and pancreatic amylase completes digestion of carbohydrates. Lipase is responsible for digestion of fatty acids and glycerol.

Aldolase is responsible for fructose intolerance. Three aldolase isozymes (A, B, and C), encoded by three different genes are differentially expressed during development. Aldolase A is found in the developing embryo and is produced in even greater amounts

Luljeta Hetemi*

Institute of Biochemistry, Ss. Cyril and Olivemedical laboratory, Prishtina, Serbia

*Corresponding author:

Luljeta Hetemi

Institute of Biochemistry, Ss. Cyril and Olivemedical laboratory, Prishtina

 hetemiluljeta@gmail.com

Tel: +38345269831

Copyright: © 2020 Hetemi L. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Citation: Hetemi L (2020) Food Intolerance and Autism. Am J Drug delv therap. Vol No: 7 Iss No: 12:25. DOI: 10.36648/2349-7211.7.12.25

in adult muscle Aldolase A deficiency has been associated with myopathy and hemolytic anemia. Aldolase A expression is repressed in adult liver, kidney and intestine and similar to aldolase C (fructose bisphosphate) levels in brain and other nervous tissue. Aldolase B is found primarily in the liver but it is also present at lower levels in kidney and intestinal cells. Aldolase B is involved in the breakdown (metabolism) of the simple sugar fructose, which is found mostly in fruits and is used in the body for energy. Aldolase C is produced in brain and other nervous tissues, and our ASD patients resulted in some fruit intolerance therefore from clinical symptoms it is doubted that they are fructose intolerant as-well. Lactase is produced in pancreas, as enzyme function is responsible for lactose intolerance. Amylase is a digestive enzyme that acts on starch in food, breaking it down into smaller carbohydrate molecules. Salivary amylase and pancreatic amylase complete digestion of carbohydrates. Protease, is in three forms of Trypsin, Pepsin, and Chymotrypsin. They complete protein digestion, producing simple amino-acids that are absorbed in circulation. Other food intolerance causes can be congenital or genetic mutation that develop from pre-natal, but in our research with ASD patients, Zinc role is very important as-well as Zinc deficiency on exocrine pancreatic activity to change the digestive function or activity. As we know Zinc deficiency has affects on the skin, nails and hair disturb in the vision, smell and taste, loss of appetite, diarrhea etc.

Low plasma Zinc levels have been associated with many psychological disorders. Schizophrenics have been shown to have decreased brain Zinc levels. Zinc deficiency could also play a role in depression. Low Zinc levels have been found in generalized anxiety disorders, panic disorders, obsessive compulsive disorders, and depression. Zinc deficiency can interfere with many metabolic processes when it occurs during infancy and childhood, a time of rapid growth and development when nutritional needs are high. Low maternal Zinc status has been associated with less attention during the neonatal period and worse motor functioning. In some studies, supplementation has been associated with motor development in very low birth weight infants. As it is known from chemistry Zn 2+ is bivalent, from it we understand that Zinc makes more vital functions from control cellular Zn, hemostasis, etc, until Zn T transporter some types, that are very important like pancreatic, paracrine, autocrine, endocrine, such as inhibiting proteasis, egzocrin, neuro endocrine also neuroegzocrin, digestive, metabolic, neurotransmitter, neuron stimulation, and for more psychosomatic and psycho-motors functions, so Zinc functions in all organism is shared in some functions as catalytic, structural, and regulatory in proteins. From basic cellular functions such as cell activations DNA replication, RNA transcription, cell divisions.

As catalytic Zn has an important function for metallo-enzymes (in our ASD patients we had higher metals results) and it is other reason that Zinc deficiency in ASD patients doesn't have the opportunity to have good function from transport, till break down of the metals. Speaking for hundreds of metabolic pathways causing numerous clinical manifestations, including impaired growth and development, and disruption of reproductive and immune function. From some researches, also resulted that Zinc deficiency is connected with gluten intolerance also food allergy, because it has an important role in Histamine and Histamine enzyme DAO. Zinc deficiency also reduces the appetite. Zinc attaches to other enzymes in the body that help break down the food. The reduction of Zinc will interrupt the digestion system, including the loss of appetite may be due to the "accumulation of undigested food inside the gastrointestinal tract".

From clinical symptoms and scientific literature and analysis indications, we prepared the laboratory panel consisting of some analysis about 50% connection with gastrointestinal system that was called follow up ASD laboratory panel on March 2018.

Initially we started with Food Intolerance test about 60 types of foods, the test is rapid blood test for determination of specific IgG4 human or Nutri-Smart test, DST –Diagnostische Systeme und Technologien GmbH. Each result, connecting clinical symptoms, with analysis of blood tests, food types, with digestive enzyme deficiency, also which types of foods were rich in digestive enzymes, clinical hyperfrenia, or hypophrenia, somatic and motoric symptoms, no social integration of ASD children, hyperactivity and more clinical informations from hetero anamnesis, that all are in connection with high level of heavy metals, Zinc deficiency, and malnutrition (because ASD patients alternate at different times to have different food preferences, ex. Banana, since it is rich in potassium, also digestive enzyme, or pineapple, milk, all from their preferences. Each of them have scientific clarifications, or toxins level in blood that speak for anxiety, non concentration, and abdominal pains, gas, diarrhea they all are big symptoms of lactose intolerance and Zinc deficiency, gastric reflux, high rates or inflammatory bowel symptoms-which is strongly linked to the mechanism and the etiology of food intolerance or some without those symptoms only gas that is connected with metan or hiper metane production who is known as one of the cause of constipation.

From more mothers with ASD children, anamnesis with them showed that they have gastrointestinal symptoms or clinical symptoms, some are tested for food intolerance and resulted positive. This makes us assume that women with positive food intolerance are the reason behind ASD children (this have one connection and with food DNA test, the new American test (May 2018), postnatal for ASD determination, that 88% confirmation the diagnosis. Which is in the process of experimentation, so our research started in January 2018.

IgG4 subclasses, or specific antibody – connection with ASD

Why IgG4 test

From more scientific literature resulted in increased IgG4 levels in children with ASD because the structure of IgG4 is different from other IgG subclasses as IgG1, IgG2, IgG3 also by contrast it has a concentration dependent half-life of as a consequence, the elimination half-life is 18–21 days, which is substantially longer than the half-life of other proteins with similar molecular weight, due to recycling by FcRn receptors. FcRn receptors are functional in most nucleated cells. These are the same receptors that transport IgG from the pregnant mother to the developing fetus in the last trimester of pregnancy. The transfer of maternal IgG to the fetal blood is an active FcRn mediated transport mechanism, so IgG1-4 subclasses resulted in the fetal serum. From several studies IgG4 related with different system disease, in our research demonstration specific related central nervous system IgG4 related with perineurial disease, vestibulochochlearis disease, hypophysitis, hyperfrenia, that are the most important connection in our ASD patients, since ASD patients are accompanied by many of these symptoms.

Preparation of the patient for testing

The first pre-analytical and pre-testing rule is that the patients do

not stop the food consumption for 3 weeks for patients that do the test for the first time, because the half plasmatic life of IgG4 is 18-21 days.

From the pre-analytical rules, the reagent test should be taken out of the refrigerator and let them sit for 30 minutes in room temperature before being tested, 30 micro-liters of capillary blood is needed then according to the prescriptive instructions with washer and diluents, we need about 50 minutes to have results.

Results and Discussion

Specific IgG 4 detection has 3 degrees:

1-st is very low detection, that does not show significant diagnostic values.

2-nd is important for diagnostic evaluation if the patient has clinical symptoms.

3-rd is the most important because it has diagnostic value. In this degree for all foods that are positive shouldn't be consumed minimum for 3 months, then in collaboration with the clinical nutritionist must diet with other foods, in order to be compensated with all the required proteins, vitamins, minerals, oligominerals, and other nutrients. From our patients, we learnt that one month after stopping the consumption of these foods, that were high intolerance, patients didn't have more clinical symptoms, and from their psychological side they looked more quiet. From all IgG subclasses, only IgG4 has the shortest half life and it has a connection with the eliminated from the diet foods when the foods stopped being consumed for 3 months, in repetition of test IgG4 detection was in level 2 after one month, and level 1 after 3 months, level one is very low detection IgG4, and it is not associated with any clinical symptomatology from hetero anamnesis.

Statistics by cases

More than 50 patients are involved in this research and 100% resulted positive for food intolerance. **Table 1.** and **Table 2.** shows the age of the patients ranges from 5 - 9 years. Approximately 30% of patients live in Prishtina, others in different cities of Kosovo.

Diet free Casein, gluten, lactose, fructose, and free other foods improve the condition of our ASD patients. For three six months that our patients eliminated these types of food that resulted intolerant positive, for example all products of free gluten, free lactose, free casein (types of milk that have casein), wheat, dry fruits, meat, eggs, etc. The patients do not have gastrointestinal symptoms. From our nutritionist we understood that the meat and egg proteins were replaced by those of plants, whereas milk of cows, sheep, goats, were replaced with almond, soya and other types of milk that do not contain casein. Fruits were replaced with the pineapple, avocado, mango and some tropical fruits that contain natural digestive enzymes.

Tropical fruits and other foods that play a major role in ASD patients with food intolerance. Pineapples contain a group of digestive enzymes called bromelain. These enzymes are proteases, which break down protein into its building blocks including amino acids. This help the digestion and absorption of proteins. Another tropical fruit that is rich with natural digestive enzyme is Papaya contains proteases that help digest the proteins.

Table 1: The most frequent intolerances resulted in about 90-95% of patients.

Casein	99%
Banana	99%
Cow's milk	99%
Goat's milk	99%
Yellow eggs	99%
Gluten	99%
Sheep's milk	98%
Dried fruit's(Almond, Hazelnut, Peanut)	98%
White egg's	97%
Tomato	96%
Wheat	96%
Rye	93%
Potato	93%
Corn	93%
Meat mix(Lamb, Mutton)	90%
Soya	85%
Cacao	81%
Apple	80%
Kiwi	80%
Mix vegetable	78%
Cheese	75%
Other foods	30%

Table 2: The age of the patients ranges from 5 - 9 years.

Age	Cities (country - Kosovo)	Other positiv tests	
5-9 years	Prishtina 30%	Zinc deficiency 20%	
	Peja 15%	Canidia positiv 15%	
	Prizren 10%	Aminoacids deficiency 13%	
	Gjilan 10%	Parasitosis 10%	
	Deqan 10%	Hypovitaminosis D 15%	
	Mitrovica 8%	Lactose intolerance 7%	
	Drenas 7%	Heavy metals higher 15%	
	Malisheva 3%	H.Pylori positiv 6%	
	Other 8%	Other 5%	

Papayas contain the digestive enzyme papain which breaks down proteins into building blocks including amino acids.

Mango Contains the digestive enzymes amylases which is a group of enzymes that break down carbs from starch (a complex carb) into sugars like glucose and maltose. The amylase enzymes in mangoes become more active as the fruit ripens.

Honey is rich in many beneficial compounds, including digestive enzymes.

The following are enzymes found in honey, particularly raw honey:

- Diastases: Break down starch into maltose
- Amylases: Break down starch into sugars like glucose and maltose
- Invertases: Break down sucrose, a type of sugar, into glucose and fructose
- Proteases: Break down proteins into amino acids.

Bananas is another fruit that contains natural digestive enzymes.

They contain amylases and glucosidases, two groups of enzymes that break down complex carbs like starch into smaller and more easily absorbed sugars. Like mangoes, these enzymes break down starch into sugars as bananas start to ripen.

Avocados Unlike other fruits, avocados are unique in that they are high in healthy fats and low in sugar. They contain the digestive enzyme lipase. This enzyme helps digest fat molecules into smaller molecules, such as fatty acids and glycerol, which are easier for the body to absorb. Lipase is also made by your pancreas, so you don't need to get it from your diet. However, taking a lipase supplement can help ease digestion, especially after a high-fat meal. Avocados also contain other enzymes, including polyphenol oxidase. This enzyme is responsible for turning green avocados brown in the presence of oxygen.

Kefir is a fermented milk beverage that is popular in the natural health community. It's made by adding kefir "grains" to milk. These "grains" are actually cultures of yeast, lactic acid bacteria and acetic acid bacteria that resemble a cauliflower. During fermentation, bacteria digest the natural sugars in milk and convert them into organic acids and carbon dioxide. This process creates conditions that help the bacteria grow but also adds nutrients, enzymes and other beneficial compounds. Kefir contains many digestive enzymes, including lipase, proteases and lactase.

Sauerkraut is a type of fermented cabbage that has a distinct sour taste. The fermentation process also adds digestive enzymes, which makes eating sauerkraut a great way to increase your intake of digestive enzymes. In addition to containing digestive enzymes, sauerkraut is also considered a probiotic food, as it contains healthy gut bacteria that boost your digestive health and immunity. Many studies have shown that consuming probiotics can ease digestive symptoms, such as bloating, gas, constipation, diarrhea and stomach pain, in both healthy adults and those with IBS, Crohn's disease and ulcerative colitis.

Kimchi is a spicy Korean side dish made from fermented vegetables. As with sauerkraut and kefir, the fermentation process adds healthy bacteria, which provide nutrients, enzymes and other benefits. Kimchi contains bacteria of the *Bacillus* species, which produce proteases, lipases and amylases. These enzymes digest proteins, fats and carbs, respectively. Aside from aiding digestion, kimchi has been linked to many other health benefits. It may be especially effective at lowering cholesterol and other heart disease risk factors.

Miso is a popular seasoning in Japanese cuisine. It's made by fermenting soybeans with salt and koji a type of fungus. Koji adds a variety of digestive enzymes, including lactases, lipases, proteases and amylases. That's one reason why miso may improve the ability to digest and absorb foods. In fact, studies have shown that the bacteria in miso can reduce symptoms linked to digestive problems, such as irritable bowel disease (IBD).

Kiwi is an edible berry that is often recommended to ease digestion. It's a great source of digestive enzymes, particularly a protease called actinidain. This enzyme helps digest proteins and is commercially used to tenderize tough meats. Scientists believe actinidain is one reason why kiwifruits seem to aid digestion. Kiwifruit contains the digestive enzyme actinidain, which helps digest proteins. Moreover, consuming kiwifruit may ease digestive symptoms like bloating and constipation.

Ginger has been a part of cooking and traditional medicine for

thousands of years. Some of ginger's impressive healthy benefits may be attributed to its digestive enzymes. Ginger contains the protease zingibain, which digests proteins into their building blocks. Digestive enzymes are proteins that break down larger molecules like fats, proteins and carbs into smaller molecules that are easier to absorb across the intestine.

Foods that contain natural digestive enzymes include pineapples, papayas, mangoes, honey, bananas, avocados, kefir, sauerkraut, kimchi, miso, kiwifruit and ginger are very well for patients with food intolerance and Autism, or ASD patients that have food intolerance.

Conclusion

This research verified the connection between Autism and food intolerance, Zinc role in pancreas and his role in digestive enzyme also verified from the treatment of diet which shows positive results, after being tested for 6 months.

References

1. Aalberse RC, Schuurman J. IgG4 breaking the rules. *Immunology*. 2002;105:9–19.
2. Aalberse RC, Gaag RV, Leeuwen J. Serologic aspects of IgG4 antibodies Prolonged immunization results in an IgG4-restricted response. *J Immunol*. 1983;130:722–726.
3. Aalberse RC, Vermeulen E. Immune reactivity to mite allergens in nonatopic subjects of immune deviation or immune ignorance. *International archives of allergy and immunology*. 2001;124:208–209.
4. Aman MG, Singh NN. *Aberrant Behavior Checklist - Community*. Slossen Educational Publications; East Aurora, NY: 1994.
5. Ashwood P, Vande Water J. A review of autism and the immune response. *Clin Dev Immunol*. 2004;11:165–174.
6. Ashwood P, Wills S, Van de Water J. The immune response in autism a new frontier for autism research. *Journal of leukocyte biology* 2006.
7. Butler MG, Dasouki MJ, Zhou XP, Talebizadeh Z, Brown M, Takahashi TN et al. Subset of individuals with autism spectrum disorders and extreme macrocephaly associated with germline PTEN tumour suppressor gene mutations. *J Med Genet*. 2005;42:318–321.
8. Cabanlit M, Wills S, Goines P, Ashwood P, Van de Water J. Brain-specific Autoantibodies in the Plasma of Subjects with Autistic Spectrum Disorder. *Ann NY Acad Sci*. 2007;1107:92–103.
9. Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children confirmation of high prevalence. *The American journal of psychiatry*. 2005;162:1133–1141.
10. Chess S. Autism in children with congenital rubella. *Journal of autism and childhood schizophrenia*. 1971;1:33–47.
11. Cohly HH, Panja A. Immunological findings in autism. *Int Rev Neurobiol*. 2005;71:317–341.
12. Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *J Child Neurol*. 1999;14:388–394.

13. Connolly AM, Chez M, Streif EM, Keeling RM, Golumbek PT, Kwon JM, et al. Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. *Biol Psychiatry*. 2006;59:354–363.

14. McElhanon BO, McCracken C, Karpen S, Sharp WG. Gastrointestinal symptoms in autism spectrum disorder a meta-analysis. *Pediatrics* (2014) 133:872–83. 10.1542/peds.2013-3995.

15. Nikolov RN, Bearss KE, Lettinga J, Erickson C, Rodowski M, Aman MG, et al. Gastrointestinal symptoms in a sample of children with pervasive developmental disorders. *J Autism Dev Disord.* (2009) 39:405–13. 10.1007/s10803-008-0637-8.

16. Croonenberghs J, Wauters A, Devreese K, Verkerk R, Scharpe S, Bosmans E et al. Increased serum albumin, gamma globulin, immunoglobulin IgG, and IgG2 and IgG4 in autism. *Psychol Med.* 2002;32:1457–1463.

17. Ferrante P, Saresella M, Guerini FR, Marzorati M, Musetti MC, Cazzullo AG. Significant association of HLA A2-DR11 with CD4 naive decrease in autistic children. *Biomed Pharmacother.* 2003;57:372–374.

18. Fortier ME, Luheshi GN, Boksa P. Effects of prenatal infection on prepulse inhibition in the rat depend on the nature of the infectious agent and the stage of pregnancy. *Behavioural brain research.* 2007;181:270–277.

19. Garbett K, Ebert PJ, Mitchell A, Lintas C, Manzi B, Mirnics K, et al. Immune transcriptome alterations in the temporal cortex of subjects with autism. *Neurobiol Dis.* 2008;30:303–311.

20. Hertz-Pannier I, Croen LA, Hansen R, Jones CR, van de Water J, Pessah IN. The CHARGE study of an epidemiologic investigation of genetic and environmental factors contributing to autism. *Environ Health Perspect.* 2006;114:1119–1125.

21. Heuer L, Ashwood P, Schauer J, Goines P, Krakowiak P, Hertz-Pannier I, et al. Reduced Levels of Immunoglobulin in Children with Autism Correlates with Behavioral Symptoms. *Autism Research Submitted* 2008.

22. Jyonouchi H, Sun S, Itokazu N. Innate immunity associated with inflammatory responses and cytokine production against common dietary proteins in patients with autism spectrum disorder. *Neuropsychobiology.* 2002;46:76–84.

23. Korvatska E, Van de Water J, Anders TF, Gershwin ME. Genetic and immunologic considerations in autism. *Neurobiol Dis.* 2002;9:107–125.

24. Kozlovskaia GV, Kliushnik TP, Goriunova AV, Turkova IL, Kalinina MA, Sergienko NS. Nerve growth factor auto-antibodies in children with various forms of mental dysontogenesis and in schizophrenia high risk group. *Zh Nevrol Psichiatr Im S S Korsakova.* 2000;100:50–52.

25. Le Couteur A, Lord C, Rutter M. *Autism Diagnostic Interview - Revised (ADI-R)* Western Psychological Services; Los Angeles: 2003.

26. Lee LC, Zachary AA, Leffell MS, Newschaffer CJ, Matteson KJ, Tyler JD, et al. HLA-DR4 in families with autism. *Pediatr Neurol.* 2006;35:303–307.

27. Lord C, Pickles A, McLennan J, Rutter M, Bregman J, Folstein S et al. Diagnosing autism: analyses of data from the Autism Diagnostic Interview. *J Autism Dev Disord.* 1997;27:501–517.

28. Lord C, Risi S, Lambrecht L, Cook EH, Jr Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord.* 2000;30:205–223.

29. Lord C, Rutter M, DiLavore PC, Risi S. *Autism Diagnostic Observation Schedule (ADOS)* Western Psychological Services; Los Angeles: 2003.

30. Meyer U, Nyffeler M, Engler A, Urwyler A, Schedlowski M, Knuesel I, et al. The time of prenatal immune challenge determines the specificity of inflammation-mediated brain and behavioral pathology. *J Neurosci.* 2006;26:4752–4762.