Immune problems in Autism and the connection between PANS and Autism

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DISCLAIMER

While Dr. Rossignol has attempted to make the information in this presentation as accurate as possible, the information is provided without any expressed or implied warranty. The purpose of this lecture is to provide information about different conditions or treatments that may affect individuals with autism and other conditions. Please be advised that Dr. Rossignol is not giving medical advice and that circumstances may dictate different treatments. All of the reviewed treatments in this lecture are considered off-label and not FDA-approved. Before beginning any treatment, please consult with your or your child’s physician.

The use of every treatment in autism is “off-label” except for Risperidone and Aripiprazole for the treatment of irritability.
Defining Autism: What is Autism?

DSM-5 emphasizes that autism is a disorder characterized by deficits in social communication and by restricted, repetitive patterns of behavior – these are subjective.

Autism is a spectrum disorder (think “autisms”) – some children are mildly affected, some are severely affected; there are probably many different causes.

Is diagnosed solely by behavioral observations.

There are no blood or other biological tests for identifying autism.

Therefore, a diagnosis of autism tells us nothing about the potential contributors or causes of the disorder.

* Important Concept *

Several metabolic abnormalities have been reported to contribute to or cause a potentially reversible form of autism.

- e.g., Cerebral Folate Deficiency

The goal is to rapidly screen for these abnormalities, identify them, and start treating them.

Testing can be done by measuring certain biomarkers (laboratory tests that may identify abnormalities).

ASD has a clear biological basis with features of known medical disorders (e.g., in my opinion, it is not just a psychiatric disorder).
A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures

First, publications were divided by several criteria, including whether or not they implicated an association between the physiological abnormality and ASD. A large percentage of publications implicated an association between ASD and immune dysregulation/inflammation (416 out of 437 publications, 95%), oxidative stress (all 115), mitochondrial dysfunction (145 of 153, 95%) and toxicant exposures (170 of 190, 89%). Second, the strength of evidence for publications in each area was computed using a validated scale. The strongest evidence was for immune dysregulation/inflammation and oxidative stress, followed by toxicant exposures and mitochondrial dysfunction. In all areas, at least 45% of the publications were rated as providing strong evidence for an association between the physiological abnormalities and ASD.

Rossignol and Frye, 2012 Mol Psychiatry 17(4): 389-401
Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism

A SYSTEMATIC REVIEW

• ASD is characterized by oxidative stress, mitochondrial dysfunction and immune dysregulation/inflammation

• Recent studies have also reported these abnormalities in brain tissue derived from individuals diagnosed with ASD.

• The brain regions found to contain these physiological abnormalities in individuals with ASD are involved in speech and auditory processing, social behavior, memory, and sensory and motor coordination.

• These findings suggest ASD has a clear biological basis with features of known medical disorders.

Rossignol and Frye, 2014 Front Physiol 5:150

Folate related problems
Folate transport into the brain

- MTHFR is the last enzyme in a cascade that produces 5-methyltetrahydrofolate (5MTHF)—this is one of the active forms of folate.
- 5MTHF binds to a Folate Receptor 1 (FR1) in the choroid plexus and then undergoes endocytosis, storage and then delivery into the CSF. It is then transported into the CSF and neurons by the reduced folate carrier (RFC).
- In this process, folate transport by FR1 is ATP-dependent.
- Low levels of 5MTHF in the brain can cause cerebral folate deficiency (CFD).
**FR Autoantibodies**

- Autoantibodies to FR1 were first reported in 2005 and can be measured in the blood.
- These autoantibodies are associated with Cerebral Folate Deficiency (CFD) syndrome, low-functioning autism, and Rett syndrome.
- Autoantibodies block the folate binding site (FR1) on the plasma surface of choroid plexus epithelial cells, impairing folate transport into the CNS.
- Without treatment, the concentration of autoantibodies increases over time.
**Blocking antibody:** 0.29 pmoles / ml serum  
**Binding Antibody:** 0.41 pmoles IgG / ml serum
Mitochondrial diseases associated with cerebral folate deficiency

A CASE SERIES

Twenty-eight patients with different mitochondrial disorders and fulfilling the previously defined diagnostic criteria were recruited from the Hospital Sant Joan de De’u, Barcelona, Spain (21 patients), the University Clinic Aachen, Germany (5 patients), and Hospital 12 de Octubre, Madrid, Spain (2 patients). Despite normal serum folate levels, 14 patients (mean age: 9.5 years; range: 3 months–34 years; Patients 1–14, table) had low CSF 5-MTHF concentrations (mean: 22.1 nmol/L; range: 0.6–48.8 nmol/L).

Garcia-Cazorla, et al., 2008  Neurology 70(16):1360-1362

Folate receptor autoimmunity and cerebral folate deficiency in low-functioning autism with neurological deficits

A CASE SERIES

Twenty-five patients with early-onset low-functioning autism with or without neurological deficits, were evaluated for serum folate, cerebrospinal fluid (CSF) 5MTHF, and serum FR autoantibodies of the blocking type to determine the significance of folate receptor (FR) autoantibodies with respect to folate transport across the blood-CSF barrier. In spite of normal serum folate, CSF 5MTHF was low in 23 of 25 patients. The reduced CSF folate in 19 of these 23 patients could be explained by serum FR autoantibodies blocking the folate binding site of the membrane-attached FR on the choroid epithelial cells. Oral folic acid supplements led to normal CSF 5MTHF and partial or complete clinical recovery after 12 months. CONTINUED...

Ramaekers et al., 2007  Neuropediatrics 38(6):276-81
Two patients (patients 2, 4) who were diagnosed early and received treatment were cured with full recovery from autism and neurological deficits. …these two patients were among the youngest and were detected at 2 years 8 months and at 3 years and 2 months. Three older patients…did not recover from autism but showed improvement of their neurological deficits. The remaining thirteen patients in the age range of three and seven years showed a good response…The partial recovery in the latter group of 13 patients consisted of amelioration of social impairment in 4 of 13 patients, reversal of impaired communication in 9 of 13 patients and disappearance of perseverative behaviour and restricted interests in 6 of 13 patients.”

Ramaekers et al., 2007  Neuropediatrics 38(6):276-81

Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial

Forty-eight children (mean age 7 years 4 months; 82% male) with ASD and language impairment were randomized to receive 12 weeks of high-dose folic acid (2 mg/kg per day, maximum 50 mg per day; n=23) or placebo (n=25). Children were subtyped by glutathione and folate receptor-alpha autoantibody (FRAA) status. Improvement in verbal communication… was significantly greater in participants receiving folic acid as compared with those receiving placebo… For FRAA-positive participants, improvement in verbal communication was significantly greater in those receiving folic acid as compared with those receiving placebo…

Frye, et al., 2018  Mol Psychiatry 23(2):247-256
Folate receptor alpha autoimmunity and cerebral folate deficiency in autism spectrum disorders

A REVIEW ARTICLE

CFD represents one of a few progressive neurological disorders that is treatable and potentially reversible. To date, 3 studies have reported an association between CFD and Rett syndrome, 7 studies have reported that CFD is associated with autism spectrum disorders (ASD) in some children, and 5 studies have reported FRα autoantibodies in children with ASD... From these studies of children with concomitant ASD and CFD, treatment with oral folinic acid... resulted in various improvements ranging from partial improvements in communication, social interaction, attention and stereotypical behavior to complete recovery of both neurological and ASD symptoms.


Decreased Brain Levels of Vitamin B12 in Aging, Autism and Schizophrenia

A BRAIN STUDY

We measured levels of five Cbl species in postmortem human frontal cortex of 43 control subjects, from 19 weeks of fetal development through 80 years of age, and 12 autistic and 9 schizophrenic subjects. Total Cbl was significantly lower in older control subjects (> 60 yrs of age), primarily reflecting a >10-fold age-dependent decline in the level of MeCbl...

In both autistic and schizophrenic subjects MeCbl and AdoCbl levels were more than 3-fold lower than age-matched controls. In autistic subjects lower MeCbl was associated with decreased MS activity and elevated levels of its substrate homocysteine (HCY).

Thirty-seven children diagnosed with autistic disorder and abnormal glutathione and methylation metabolism were treated with twice weekly 75 microg/Kg methylcobalamin and twice daily 400 microg folic acid for 3 months.

<table>
<thead>
<tr>
<th>Vineland Subscale</th>
<th>Baseline Age Equivalent Months (mean ± SE)</th>
<th>Post-Intervention Age Equivalent Months (mean ± SE)</th>
<th>Change (months) (mean; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptive Language</td>
<td>23.1 ± 1.8</td>
<td>31.4 ± 3.4</td>
<td>8.3 (2.9, 13.7)</td>
</tr>
<tr>
<td>Expressive Language</td>
<td>20.6 ± 1.9</td>
<td>27.5 ± 2.9</td>
<td>6.0 (3.3, 9.4)</td>
</tr>
<tr>
<td>Written Language</td>
<td>40.5 ± 3.8</td>
<td>46.7 ± 4.0</td>
<td>6.2 (3.4, 9.0)</td>
</tr>
<tr>
<td>Personal Skills</td>
<td>30.5 ± 2.3</td>
<td>40.5 ± 3.8</td>
<td>10.0 (3.8, 16.2)</td>
</tr>
<tr>
<td>Domestic Skills</td>
<td>30.3 ± 4.1</td>
<td>39.3 ± 5.9</td>
<td>9.0 (-1.4, 19.4)</td>
</tr>
<tr>
<td>Community Skills</td>
<td>32.9 ± 2.9</td>
<td>36.1 ± 3.8</td>
<td>2.0 (-3.0, 6.9)</td>
</tr>
<tr>
<td>Interpersonal Skills</td>
<td>18.7 ± 2.7</td>
<td>24.1 ± 3.9</td>
<td>5.4 (0.0, 10.9)</td>
</tr>
<tr>
<td>Play/Leisure Skills</td>
<td>22.0 ± 4.5</td>
<td>34.0 ± 4.1</td>
<td>12.0 (4.1, 19.6)</td>
</tr>
<tr>
<td>Coping Skills</td>
<td>25.8 ± 2.5</td>
<td>34.3 ± 4.0</td>
<td>11.5 (4.9, 18.0)</td>
</tr>
</tbody>
</table>


Randomized, Placebo-Controlled Trial of Methyl B12 for Children with Autism

A total of 57 children with ASD were randomly assigned to 8 weeks of treatment with methyl B12 (75 mug/kg) or saline placebo every 3 days in a subcutaneous injection. RESULTS: A total of 50 children (mean age 5.3 years, 79% male) completed the study. The primary outcome measure - the clinician rated CGI-I score - was statistically significantly better (lower) in the methyl B12 group (2.4) than in the placebo group (3.1)... Clinical improvement among children treated with methyl B12 was positively correlated with increases in plasma methionine (p = 0.05), decreases in S-adenosyl-L-homocysteine (SAH) (p = 0.007)... indicating an improvement in cellular methylation capacity.

Hendren, et al., 2016  J Child Adolesc Psychopharmacol 26(9):774-783
Interleukin-17 (IL-17)-mediated immune responses play a crucial role in the mucosal host defence against microbial and fungal pathogens. However, the chronic activation of IL-17-producing T helper cells can cause autoimmune disease. In addition, recent studies have highlighted key roles of innate cell-mediated IL-17 responses in various inflammatory settings. Besides inflammation, there have also been intriguing findings regarding the involvement of IL-17 responses in the pathogenesis of cardiovascular diseases and tumour formation. Here, we discuss the latest discoveries in regulation and function of innate and adaptive IL-17-producing cells.

Hirota, et al., 2012  EMBO Rep 13(2):113-120
**Targeting IL-17 and TH17 cells in chronic inflammation**

**IL-17 and tumour necrosis factor**

alpha combination induces a HIF-1alpha-dependent invasive phenotype in synoviocytes

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A functional DNA binding assay was used to evaluate the regulation of the key hypoxia-related gene hypoxia-inducible factor 1 (HIF-1alpha) expression and activation… **RESULTS:** Among the genes induced by **IL-17A** in RA synoviocytes, a molecular pattern of **inflammation hypoxia-related genes**, including CXC chemokine receptor 4 (CXCR4) and MMP2 was identified. Using immunofluorescence microscopy, the expression of CXCR4 was confirmed on synoviocytes. IL-17A and TNFalpha induced synoviocyte migration and invasion through a CXCR4-dependent mechanism with a synergistic effect. Their combination **activated HIF-1alpha** through the nuclear factor kappaB pathway. IL-17 enhanced invasion through MMP2 induction as demonstrated using siRNA. Finally, hypoxia genes were overexpressed in the blood of RA patients.

**Hot, et al., 2012 Ann Rheum Dis 71(8):1393-1401**

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**Figure 2 | Key functions of IL-17 and its role in inflammation and matrix destruction.** Interleukin-17 (IL-17) acts on various cellular targets, leading to cell activation. The effect of IL-17 on endothelial cells leads to inflammation and procoagulant activity. When acting on epithelial cells and fibroblasts, IL-17 leads to cytokine and enzyme production. On macrophages and dendritic cells, IL-17 contributes to inflammation by increasing the production of pro-inflammatory cytokones. In the context of joint inflammation, a process that involves osteoblasts and chondrocytes, IL-17 activates matrix destruction in cartilage and bone. CCL20, chemokine CC motif ligand 20; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; MMP, matrix metalloproteinase; RANKL, receptor activator of NF-κB ligand; T, T helper; TNF, tumour necrosis factor.
Recently T-helper 17 (Th17) cells were demonstrated to disrupt the blood-brain barrier (BBB) by the action of IL-17A. The aim of the present study was to examine the mechanisms that underlie IL-17A-induced BBB breakdown... Experimental autoimmune encephalomyelitis (EAE) was induced in C57BL/6 mice. IL-17A induced NADPH oxidase- or xanthine oxidase-dependent reactive oxygen species (ROS) production. The resulting oxidative stress activated the endothelial contractile machinery, which was accompanied by a down-regulation of the tight junction molecule occludin. Blocking either ROS formation or myosin light chain phosphorylation or applying IL-17A-neutralizing antibodies prevented IL-17A-induced BBB disruption...

These observations indicate that IL-17A accounts for a crucial step in the development of EAE by impairing the integrity of the BBB, involving augmented production of ROS.

Huppert, et al., 2010  FASEB J 24(4):1023-1034

Potential causes of increased IL-17
Linking the Human Gut Microbiome to Inflammatory Cytokine Production Capacity

Schirmer, et al., 2016  Cell 167(4):1125-1136.e1128

Anti-Candida albicans IgG
Antibodies in Children With Autism Spectrum Disorders

Increases in fungal species such as Candida albicans are associated with inflammatory bowel disorders, and have recently been implicated in several neurological disorders including schizophrenia. We aimed to determine if children with ASD exhibit elevations in antibodies that target C. albicans, indicating current or previous overgrowth of this fungal species. We measured anti-C. albicans immunoglobulin (IgG) in plasma from 80 children enrolled in the UC Davis MIND Institute CHARGE study. Measurements were acquired using a commercial ELISA kit. Plasma anti-C. albicans antibody positivity was found in 36.5% (19/52) of children with ASD. Anti-C. albicans antibodies in typically developing controls was (14.3%; 4/28). Overall, ASD children had a higher rate of high-positive values compared to typically developed children with an unadjusted odds ratio of 3.45 (95% confidence interval, 1.0409 to 11.4650; p = 0.041, two-tailed). GI dysfunction was found in about half of the ASD children who were positive for anti-Candida IgG. This study provides evidence of a new microbial risk factor for ASD.

Hughes and Ashwood, 2018  Front Psychiatry 9:627
Distinct Microbiome-Neuroimmune Signatures Correlate With Functional Abdominal Pain in Children With Autism Spectrum Disorder

**METHODS:** Because commensal clostridia interactions with the intestinal mucosa can regulate disease-associated cytokine and serotonergic pathways in animal models, we evaluated whether microbiome-neuroimmune profiles (from rectal biopsy specimens and blood) differed in ASD children with functional gastrointestinal disorders (ASD-FGID, n = 14) compared with neurotypical (NT) children with FGID (NT-FGID, n = 15) and without abdominal pain (NT, n = 6). Microbial 16S ribosomal DNA community signatures, cytokines, and serotonergic metabolites were quantified and correlated with gastrointestinal symptoms. **RESULTS:** A significant increase in several mucosa-associated Clostridiales was observed in ASD-FGID, whereas marked decreases in Dorea and Blautia, as well as Sutterella, were evident. Stratification by abdominal pain showed multiple organisms in ASD-FGID that correlated significantly with cytokines (interleukin [IL]6, IL1, IL17A, and interferon-gamma).


| Table 4. Cytokine Correlations With Bacteria Significantly Associated With the ASD-FGID Group |
|---------------------------------|----------------|---------|
| Specimen | Organism | Cytokine | R   | P value |
| Serum | C. albensis | IL7 | 0.662 | .011 | \(\uparrow\) |
| Biopsy | C. butyricum | IL1A | 0.739 | .009 | \(\downarrow\) |
| Serum | C. butyricum | IL12p70 | 0.969 | .000 | \(\downarrow\) |
| Serum | C. butyricum | IL17A | 0.703 | .027 | \(\downarrow\) |
| Serum | C. butyricum | IL10 | 0.966 | .000 | \(\downarrow\) |
| Serum | C. butyricum | IL5 | 0.903 | .000 | \(\downarrow\) |
| Serum | C. butyricum | IL6 | 0.972 | .000 | \(\downarrow\) |
| Serum | C. butyricum | IP-10 | 0.605 | .019 | \(\downarrow\) |
| Serum | C. butyricum | MCP-1 | 0.813 | .001 | \(\downarrow\) |
| Serum | C. butyricum | MCP-3 | 0.805 | .000 | \(\downarrow\) |
| Serum | C. butyricum | VEGF | 0.743 | .018 | \(\downarrow\) |
| Serum | L. corynalis | IFN-α/β | 0.712 | .024 | \(\downarrow\) |
| Serum | L. fermentum | IL15 | 0.582 | .035 | \(\downarrow\) |
| Serum | L. fermentum | IL9 | 0.729 | .016 | \(\downarrow\) |
| Serum | L. fermentum | IL-1β | 0.023 | .033 | \(\downarrow\) |
| Serum | L. fermentum | IL7 | 0.643 | .013 | \(\downarrow\) |
| Serum | P. pleciti | Gm-CSF | 0.783 | .003 | \(\downarrow\) |
| Serum | P. pleciti | IL9 | 0.708 | .090 | \(\downarrow\) |
| Biopsy | T. penneri, species | VEGF | 0.604 | .031 | \(\downarrow\) |
| Serum | T. penneri, species | IL1α | 0.969 | .000 | \(\downarrow\) |
| Serum | T. penneri, species | TNF-α | 0.967 | .020 | \(\downarrow\) |
| Serum | D. rectogenitalis | IL12p70 | 0.766 | .000 | \(\downarrow\) |
| Serum | S. succinatores | IL12p70 | 0.860 | .003 | \(\downarrow\) |

*After multiple testing correction (Benjamini–Hochberg).*

Dysregulation of intestinal IL17 signaling & the microbiome exacerbate autoimmune neuroinflammation

We hypothesized that disruption of the reciprocal regulatory relationship between enteric IL-17 signaling and the gut microbiota leads to dysbiosis, expansion of Th17 cells, and increased predisposition to autoimmune neuroinflammation. Our data suggested that Il17ra/rcfl/fl x villin cre+ mice, which have higher SFB levels, exhibit earlier EAE onset and increased EAE severity and incidence as compared to littermate cre− controls. Treatment with vancomycin ameliorated disease, further supporting our hypothesis. In addition, preliminary data indicated that cre+ mice have increased CCR2 and CCR6 gut expression at baseline. At day 9-post immunization in the same mice, there was increased expression of CCR2 and Nox2 in the spinal cord and Csf2 in the gut. Together, this suggested that there could be increased migration into the CNS of cre+ mice, contributing to exacerbated disease.

Castillo, et al., 2016 The Journal of Immunology 196(1 Supplement):118.114-118.114

IL-17 and autism
Elevated serum levels of interleukin-17A in children with autism

BACKGROUND: The T-helper (Th)1/Th2 dichotomy dominated the field of immune regulation until interleukin (IL)-17-expressing T cells (Th17) were proposed to be a third lineage of helper T cells, the key players in the pathogenesis of autoimmune disorders. Autoimmunity to brain tissue may play a pathogenic role in autism. **IL-17A is a pro-inflammatory cytokine** that has been shown to play an important role in various autoimmune neuroinflammatory diseases. The aim of this study was to measure serum levels of IL-17A in relation to the degree of the severity of autism. METHODS: Serum IL-17A levels were measured by ELISA in 45 children with autism and 40 matched healthy controls. RESULTS: Children with autism had significantly higher serum IL-17A levels than healthy controls (P <0.001), with increased serum levels of IL-17A found in 48.9% of the autism group. Patients with severe autism had significantly higher serum IL-17A levels than those with mild to moderate autism (P=0.01), and raised serum IL-17A levels were significantly more common in children with severe autism (67.9%) than in those with mild to moderate autism (17.6%), P=0.001.

Al-Ayadhi and Mostafa, 2012  J Neuroinflammation 9(1):158

Activation of IL-17 receptor leads to increased oxidative inflammation in peripheral monocytes of autistic children

Several studies have shown an increased expression/release of Th17 related cytokine, IL-17A in ASD. **IL-17A may enhance neuroinflammation** via its IL-17A receptor, i.e. IL-17RA expressed in immune cells (such as monocytes) of autistic children. Increased oxidative stress has been implicated in a number of neuropsychiatric disorders including ASD… Our study shows that ASD individuals have increased IL-17RA expression in monocytes which is associated with increased nuclear factor kappa-light-chain-enhancer of activated B cells (NFkappaB) pathway and inducible nitric oxide synthase (iNOS)/nitrotyrosine expression as compared to typically developing children. Moreover, in vitro activation of IL-17 receptor by IL-17A in monocytes isolated from ASD individuals leads to enhanced iNOS expression via NFkappaB pathway. IL-17RA antibody treatment in vitro reversed IL-17A-induced increase in NFkappaB and iNOS/nitrotyrosine expression in monocytes isolated from ASD subjects.

Nadeem, et al., 2018  Brain Behav Immun 67:335-344
Prenatal exposure to **maternal immune activation** (MIA) has been implicated as an environmental risk factor for ASD... Recent evidence points to a potential inflammation pathway linking MIA-associated ASD with the activity of T helper 17 (Th17) lymphocytes and their effector cytokine **interleukin-17A (IL-17A)**. IL-17A has been implicated from human studies and elevated IL-17A levels in the blood have been found to correlate with phenotypic severity in a subset of ASD individuals. In MIA model mice, elevated IL-17A levels also have been observed. Additionally, antibody blockade to inhibit IL-17A signaling was found to prevent ASD-like behaviors in offspring exposed to MIA. Therefore, IL-17A dysregulation may play a causal role in the development of ASD.

Wong and Hoeffer, 2018  Exp Neurol 299(Pt A):228-240

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**IL-17 in PANS**
Serum Cytokine Profiles of Children with Obsessive-Compulsive Disorder Shows the Evidence of Autoimmunity

RESULTS: Interleukin-17A, tumor necrosis factor-alpha, and interleukin-2 levels were significantly higher in obsessive compulsive disorder patients. However, there was no correlation between T helper 1 and 17 cytokine profiles in the obsessive compulsive disorder group. The duration and severity of obsessive compulsive disorder symptoms were not significantly associated with interleukin-17A, interferon-gamma, interleukin-10, interleukin-6, interleukin-4, and interleukin-2 levels. Interestingly, a negative correlation was found between tumor necrosis factor-alpha levels and Clinical Global Impression scores. CONCLUSIONS: These findings suggest, in some cases, obsessive compulsive disorder may develop on a background of autoimmunity, and interleukin-2, tumor necrosis factor-alpha, and interleukin-17A may play a role in these autoimmune processes. Therefore, we believe it is important to investigate for obsessive compulsive disorder symptoms in patients with autoimmune disease and, conversely, autoimmune diseases in obsessive compulsive disorder patients.

Simsek, et al., 2016  Int J Neuropsychopharmacol 19(8)

Group A Streptococcus intranasal infection promotes CNS infiltration by streptococcal-specific Th17 cells

Group A streptococcal (GAS) infection induces the production of Abs that cross-react with host neuronal proteins, and these anti-GAS mimetic Abs are associated with autoimmune diseases of the CNS. However, the mechanisms that allow these Abs to cross the blood-brain barrier (BBB) and induce neuropathology remain unresolved. We have previously shown that GAS infection in mouse models induces a robust Th17 response in nasal-associated lymphoid tissue (NALT). Here, we identified GAS-specific Th17 cells in tonsils of humans naturally exposed to GAS, prompting us to explore whether GAS-specific CD4+ T cells home to mouse brains following i.n. infection. Intranasal challenge of repeatedly GAS-inoculated mice promoted migration of GAS-specific Th17 cells from NALT into the brain, BBB breakdown, serum IgG deposition, microglial activation, and loss of excitatory synaptic proteins under conditions in which no viable bacteria were detected in CNS tissue.

In particular, they reported the presence of **group A streptococcal specific Th17 lymphocytes** in tonsils of humans previously exposed to natural GABHS infections (Dileepan et al., 2016). Repeated intranasal (i.n.) inoculations of GABHS in mice triggered the expansion of Th17 cells and the production of **interleukin 17 (IL17)**, as shown in a previous study (Dileepan et al., 2011). IL17 causes the **damaging of BBB barrier** through the production of reactive oxygen species (ROS) in endothelial cells (Kebir et al., 2007; Huppert et al., 2010). Dileepan et al. (2016) repeatedly inoculated mice i.n. with GABHS to investigate if exposure to streptococcus induces Th17 GABHS-specific cells enter the mice brain. They reported that group A streptococcal infections trigger in mice a lymphocyte Th17 response together with the production of IL-17A in nasal-associated lymphoid tissue (NALT).
Oral probiotic administration during pregnancy prevents autism-related behaviors in offspring induced by maternal immune activation via anti-inflammation in mice.

Maternal immune activation (MIA) is associated with an increased risk for autism spectrum disorders (ASD) in offspring. Animal experiments have found that interleukin 6 (IL-6) and IL-17a are key cytokines in the induction of ASD by MIA. Moreover, probiotics were verified to inhibit the production of proinflammatory cytokines. Therefore, we investigated whether the administration of oral probiotics during pregnancy might protect the offspring that have suffered MIA from developing ASD. Probiotics were orally administered to pregnant mice with/without the simultaneous administration of Poly(I:C). We found that oral probiotics prevented the ASD-like behaviors induced by MIA in offspring. Furthermore, oral probiotics prevented the MIA-induced increases in the IL-6 and IL-17a levels in both maternal serum and fetal brains, parvalbumin positive (PV(+)) neuron loss, and the decrease in the gamma-aminobutyric acid levels in the prefrontal cortex of adult offspring...

In the present study, the effect of resveratrol administration (20 and 40 mg/kg) was evaluated in both BTBR and C57BL/6 (B6) mice. Behavioral (self-grooming), Foxp3, T-bet, GATA-3, RORgammat, and IL-17A in CD4+ T cells were assessed. Our study showed that BTBR control mice exhibited a distinct immune profile from that of the B6 control mice. BTBR mice were characterized by lower levels of Foxp3+ and higher levels of RORgammat+, T-bet+, and GATA-3+ production in CD4+ T cells when compared with B6 control. Resveratrol (20 and 40 mg/kg) treatment to B6 and BTBR mice showed substantial induction of Foxp3+ and reduction of T-bet+, GATA-3+, and IL-17A+ expression in CD4+ cells when compared with the respective control groups.

Bakheet, et al., 2017  Mol Neurobiol 54(7):5201-5212

Sulforaphane activates Nrf2 and thus is considered a potential approach to treat several neurological disorders including autism. In the current work, we used sulforaphane in asocial BTBR mice and its social counterpart C57/BL6 (C57) mice to assess its therapeutic potential and molecular mechanisms (Th17 immune responses, and oxidant-antioxidant balance) through which it acts. Our results demonstrate that BTBR treated with sulforaphane had reduced self-grooming/marble burying behavior, and increased social interaction in three chambered sociability test as compared to untreated BTBR mice. Further, sulforaphane-treated BTBR mice had reduced Th17 immune responses (STAT3, RORC, IL-17 A and IL-23R expression in CD4 + T cells), oxidative stress parameters in neutrophils/cerebellum (NFkB, iNOS, and lipid peroxides). Furthermore, sulforaphane-treated BTBR and C57 mice had upregulated enzymatic antioxidant defenses in neutrophils/cerebellum (SOD, GPx and GR expression and activity).

Nadeem, et al., 2019  Behav Brain Res 364:213-224
Reduced Pro-Inflammatory Cytokines after Eight Weeks of Low-Dose Naltrexone for Fibromyalgia

In this 10-week, single-blind, crossover trial we tested the immune effects of eight weeks of oral administration of low-dose naltrexone (LDN). We enrolled eight women with an average age of 46 years, symptom severity of 62 out of 100, and symptom duration of 14 years. We found that LDN was associated with reduced plasma concentrations of interleukin (IL)-1beta, IL-1Ra, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p40, IL-12p70, IL-15, IL-17A, IL-27, interferon (IFN)-alpha, transforming growth factor (TGF)-alpha, TGF-beta, tumor necrosis factor (TNF)-alpha, and granulocyte-colony stimulating factor (G-CSF). We also found a 15% reduction of FM-associated pain and an 18% reduction in overall symptoms.

Parkitny and Younger, 2017 Biomedicines 5(2)

T helper 1 response is correlated with widespread pain, fatigue, sleeping disorders and the quality of life in patients with fibromyalgia and is modulated by hyperbaric oxygen therapy

METHODS: Patients with primary FM and controls were treated with HBOT. Physical, emotional and social assessment, quality of sleep, tender points, intensity score, WPI and symptom severity were evaluated before and after HBOT. Furthermore, a characterisation of CD4 T lymphocytes and their cytokine production was performed by flow cytometry. The expression of TNF-alpha, IFN-gamma, IL-17, IL-9 and IL-22 was also assessed by RT-PCR. Finally, the serum levels of serotonin were evaluated by ELISA. RESULTS: Our results confirm the participation of immune system in the pathogenesis of FM and highlight the impact of HBOT treatment, with particular regard to the changes on proinflammatory cytokines production by CD4 T cells subsets. CONCLUSIONS: FM patients show a Th1 signature and the activation of this subset is modulated by HBOT.

Supplements

- Omega 3 fish oil
- Zinc
- Sulforaphane
- Vitamin A
- Vitamin D3
- Folate
- Chromium
- Melatonin
- GABA
- Probiotics
- Curcumin
- Berberine
- Ursolic acid
- Chinese Skullcap
- Grape seed extract
- Galantamine
- Butyrate
- Resveratrol
- Ginger
- Cyanidin
- Low lectin diet

C-type lectins, fungi and Th17 responses

Th17 cells are a recently discovered subset of T helper cells characterised by the release of IL-17, and are thought to be important for mobilization of immune responses against microbial pathogens, but which also contribute to the development of autoimmune diseases. The identification of C-type lectin receptors which are capable of regulating the balance between Th1 and Th17 responses has been of particular recent interest, which they control, in part, though the release of Th17 inducing cytokines. Many of these receptors recognise fungi, and other pathogens, and play key roles in driving the development of protective anti-microbial immunity. Here we will review the C-type lectins that have been linked to Th17 type responses and will briefly examine the role of Th17 responses in murine and human anti-fungal immunity.

Vautier, et al., 2010  Cytokine Growth Factor Rev 21(6):405-412
Lectins

- Legumes, such as beans, peas, lentils, and peanuts
- Squash
- Nightshade vegetables, such as eggplant, peppers, potatoes, and tomatoes
- Grains
- Corn
- A1 milk

Other Potential Immune Related Treatments: Medications
Medications: Anti-inflammatory and Other Treatments

• Valtrex
• Transfer Factor
• Propranolol
• Microbiota Transfer Therapy
• Naltrexone
• Celecoxib
• Pentoxifylline
• Minocycline
• Spironolactone
• Steroids
• Intravenous Immunoglobulin (IVIG)
• Hyperbaric Oxygen Therapy (HBOT)

Antiherpes virus-specific treatment and cognition in schizophrenia: a test-of-concept randomized double-blind placebo-controlled trial

METHODS: Using a double-blind placebo-controlled design, we randomized 24 HSV1-seropositive schizophrenia subjects to receive either valacyclovir (n = 12) or placebo (n = 12) for 18 weeks in addition to stable doses of APs. Valacyclovir dose was stabilized at 1.5 g twice daily orally. RESULTS: Valacyclovir group improved in verbal memory, working memory, and visual object learning compared with placebo group. The effect sizes (Cohen's d) were 0.79 for working memory, 1.14 for immediate verbal memory, and 0.97 for the visual object learning. Psychotic symptom severity did not improve. CONCLUSIONS: Supplemental valacyclovir may alleviate impairments in cognitive domains that are often observed in schizophrenia but not psychotic symptoms in those exposed to HSV1.

Transfer factor immunotherapy of an autistic child with congenital cytomegalovirus

Brief Report

Transfer Factor Immunotherapy of an Autistic Child with Congenital Cytomegalovirus

E. Gene Stubbs and Sarojini S. Budden
University of Oregon Health Sciences Center
Denis R. Burger and Arthur A. Vandenbark
Veterans Administration Hospital, Portland


Treatment of viral encephalitis organic personality disorder and autistic features with propranolol: a case report

Schmidt, et al., 1995 Neurorehabilitation and Neural Repair 9(1): 41-45

Objective: To observe and describe the clinical effects of propranolol in an agitated and violent patient with postviral encephalitis organic personality disorder. Background: Cognitive and behavioral deficits are common in patients with viral encephalitis. Methods to modify behavior by a behavior program and medication have reported limited success. Case: A sixteen-year-old girl developed progressive violent and sexually disinhibited behavior five weeks following acute viral encephalitis (presumed herpes simplex encephalitis). Three weeks of high dose lorazepam (6 mg/d) failed to control her symptoms. Intensive behavioral therapy was also ineffective and violent behavior increased during structured treatment hours. Benzodiazepines and low dose haloperidol were ineffective over the subsequent two weeks in a neurorehabilitation unit. Propranolol was then given (10 mg b.i.d. to 20 mg t.i.d.) and she had a dramatic change in behavior with less violence and less agitation after one day of treatment with propranolol. Her short-term memory improved. Decreased dosage of propranolol was associated with the return of violent behavior. Maintenance propranolol was effective in controlling her symptoms and led to the resumption of her multidisciplinary rehabilitation program. Conclusion: Violent and autistic behavior due to viral (herpes) encephalitis may respond to propranolol. Key Words: Propranolol—Viral encephalitis—Organic personality disorder—Autism.
Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Here, a small open-label clinical trial evaluated the impact of Microbiota Transfer Therapy (MTT) on gut microbiota composition and GI and ASD symptoms of 18 ASD-diagnosed children. RESULTS: MTT involved a 2-week antibiotic treatment, a bowel cleanse, and then an extended fecal microbiota transplant (FMT) using a high initial dose followed by daily and lower maintenance doses for 7-8 weeks. The Gastrointestinal Symptom Rating Scale revealed an approximately 80% reduction of GI symptoms at the end of treatment, including significant improvements in symptoms of constipation, diarrhea, indigestion, and abdominal pain. Improvements persisted 8 weeks after treatment. Similarly, clinical assessments showed that behavioral ASD symptoms improved significantly and remained improved 8 weeks after treatment ended. Bacterial and phagedeep sequencing analyses revealed successful partial engraftment of donor microbiota and beneficial changes in the gut environment. Specifically, overall bacterial diversity and the abundance of Bifidobacterium, Prevotella, and Desulfovibrio among other taxa increased following MTT, and these changes persisted after treatment stopped (followed for 8 weeks).

Kang, et al., 2017 Microbiome 5(1):10

Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota

We previously performed an open-label trial of Microbiota Transfer Therapy (MTT) that combined antibiotics, a bowel cleanse, a stomach-acid suppressant, and fecal microbiota transplant, and observed significant improvements in GI symptoms, autism-related symptoms, and gut microbiota. Here, we report on a follow-up with the same 18 participants two years after treatment was completed. Notably, most improvements in GI symptoms were maintained, and autism-related symptoms improved even more after the end of treatment. Important changes in gut microbiota at the end of treatment remained at follow-up, including significant increases in bacterial diversity and relative abundances of Bifidobacteria and Prevotella. Our observations demonstrate the long-term safety and efficacy of MTT as a potential therapy to treat children with ASD who have GI problems, and warrant a double-blind, placebo-controlled trial in the future.

Low-dose naltrexone for disease prevention and quality life

The use of low-dose naltrexone (LDN) for the treatment and prophylaxis of various bodily disorders is discussed. Accumulating evidence suggests that LDN can promote health supporting immune-modulation which may reduce various oncogenic and inflammatory autoimmune processes. Since LDN can upregulate endogenous opioid activity, it may also have a role in promoting stress resilience, exercise, social bonding, and emotional well-being, as well as amelioration of psychiatric problems such as autism and depression. It is proposed that LDN can be used effectively as a buffer for a large variety of bodily and mental ailments through its ability to beneficially modulate both the immune system and the brain neurochemistries that regulate positive affect.


Efficacy and Safety of Naltrexone Use in Pediatric Patients with Autistic Disorder

Three case reports, 8 case series, and 14 clinical studies were identified as pertinent.

Data Synthesis
Naltrexone has been used most commonly at doses ranging from 0.5 to 2 mg/kg/day and found to be predominantly effective in decreasing self-injurious behavior. Naltrexone may also attenuate hyperactivity, agitation, irritability, temper tantrums, social withdrawal, and stereotyped behaviors. Patients may also exhibit improved attention and eye contact. Transient sedation was the most commonly reported adverse event. Small sample size, short duration, and inconsistent evaluative methods characterize the available research.

Conclusions
A child affected by AD may benefit from a trial of naltrexone therapy, particularly if the child exhibits self-injurious behavior and other attempted therapies have failed. Serious adverse effects have not been reported in short-term studies.

Elchaar et al., 2006 Ann Pharmacother 40(6): 1086-95
Celecoxib as adjunctive treatment to risperidone in children with autistic disorder: A randomized, double-blind, placebo-controlled trial

Methods
In a 10-week randomized double-blind placebo-controlled study, 40 outpatient children with a diagnosis of autism were randomly allocated to celecoxib plus risperidone or placebo plus risperidone. The dose of risperidone and celecoxib were titrated up to 3 and 300 mg/day, respectively.

Results
By week 10, patients in the celecoxib group showed significantly greater improvement in the Irritability (P < 0.001), Lethargy/Social Withdrawal (P < 0.001), and Stereotypic Behavior (P < 0.00) but not in Hyperactivity/Noncompliance (P = 0.202) and Inappropriate Speech (P = 0.802) subscales than the placebo group.


Double-blind, placebo-controlled trial of pentoxifylline added to risperidone: Effects on aberrant behavior in children with autism

Methods
Forty children between the ages 4 and 12 years with a DSM IV-TR clinical diagnosis of autism were recruited. The children presented with a chief complaint of severely disruptive symptoms related to autistic disorder. Patients were randomly allocated to pentoxifylline+risperidone or placebo+risperidone for a 10-week, double-blind, placebo-controlled study. The dose of risperidone was titrated up to 3 mg/day, pentoxifylline was titrated to 600 mg/day. Patients were assessed at baseline and after 2, 4, 6, 8 and 10 weeks of starting medication. The measure of the outcome was the Aberrant Behavior Checklist-Community (ABC-C).

Results
The difference between the two protocols was significant as the group that received pentoxifylline had greater reduction in ABC-C subscale scores for Irritability, Lethargy/Social Withdrawal, Stereotypic Behavior, Hyperactivity/Noncompliance and Inappropriate Speech.

Akhondzadeh et al., 2010 Prog Neuropsychopharmacol Biol Psychiatry 34(1): 32-6
A pilot open-label trial of minocycline in patients with autism and regressive features

Methods

Eleven children were enrolled in an open-label trial of six months of minocycline (1.4 mg/kg). Ten children completed the trial.

Results

Clinical improvements were negligible. The laboratory assays demonstrated significant changes in the expression profile of the truncated form of brain derived neurotrophic factor (BDNF) \((P = 0.042)\) and hepatic growth factor (HGF) \((P = 0.028)\) in CSF. Only the chemokine CXCL8 (IL-8) was significantly different \((P = 0.047)\) in serum while no significant changes were observed in CSF or serum in chemokines such as CCL2 (MCP-1) or cytokines such as TNF-alpha, CD40L, IL-6, IFN-gamma and IL-1beta when pre- and post-treatment levels of these proteins were compared. No significant pre- and post-treatment changes were seen in the profiles of plasma metalloproteinases, putative targets of the effects of minocycline.

Pardo et al., 2013 J Neurodev Disord 5(1): 9

<table>
<thead>
<tr>
<th>pg/ml</th>
<th>TNFα</th>
<th>TGFβ</th>
<th>IP10</th>
<th>IL6</th>
<th>MCP-1</th>
<th>IL1β</th>
<th>MIP1β</th>
<th>IL10</th>
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<tr>
<td>CSF</td>
<td>81</td>
<td>1632</td>
<td>150</td>
<td>0</td>
<td>242</td>
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<td>Serum</td>
<td>0</td>
<td>12527</td>
<td>21</td>
<td>3</td>
<td>665</td>
<td>3</td>
<td>37</td>
<td>0</td>
</tr>
</tbody>
</table>
A Randomized Double-Blind, Placebo-Controlled Trial of Minocycline in Children and Adolescents with Fragile X Syndrome

Randomized, double-blind, placebo-controlled, crossover trial in individuals with FXS, aged 3.5 years to 16 years (n = 55, mean age 9.2 [SD, 3.6] years). Participants were randomized to minocycline or placebo for 3 months and then switched to the other treatment.

Results
Sixty-nine subjects were screened and 66 were randomized. Fifty-five subjects (83.3%) completed at least the first period and 48 (72.7%) completed the full trial. Intention-to-treat analysis demonstrated significantly greater improvements in one primary outcome, Clinical Global Impression Scale-Improvement after minocycline compared with placebo (2.49 +/- 0.13 and 2.97 +/- 0.13, respectively, p = .0173) and greater improvement in ad hoc analysis of anxiety and mood-related behaviors on the Visual Analog Scale (minocycline: 5.26 cm +/- 0.46 cm, placebo: 4.05 cm +/- 0.46 cm; p = .0488).

Leigh et al., 2013  J Dev Behav Pediatr 34(3): 147-155

Minocycline as Adjunctive Treatment to Risperidone in Children with Autistic Disorder: A Randomized, Double-Blind Placebo-Controlled Trial

METHODS: Forty-six children with diagnosis of autistic disorder … who were already drug-free for at least 6 months participated in a randomized controlled trial and underwent 10 weeks of treatment with either minocycline (50 mg twice per day) or placebo in addition to risperidone titrated up to 2 mg/day (based on bodyweight). RESULTS: General linear model repeated measures showed significant effect for time x treatment interaction on the irritability [F(2, 88) = 3.94, p = 0.02] and hyperactivity/noncompliance [F(1.50, 66.05) = 7.92, p = 0.002], but not for lethargy/social withdrawal [F(1.61, 71.02) = 0.98, p = 0.36], stereotypic behavior [F(1.34, 58.80) = 1.55, p = 0.22], and inappropriate speech subscale scores [F(1.52, 66.88) = 1.15, p = 0.31]. By week 10, 21 (91.3%) patients in the minocycline group and 15 (65.5%) patients in the placebo group achieved at least partial response (p = 0.03). Frequencies of adverse events were not significantly different between groups.

Ghaleiha, et al., 2016  J Child Adolesc Psychopharmacol 26(9):784-791
Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders

Spironolactone is an aldosterone antagonist and potassium-sparing diuretic with a desirable safety profile. It possesses potent anti-inflammatory and immune modifying properties that might make it an excellent medical intervention for autism spectrum disorders. Furthermore, spironolactone demonstrates substantial anti-androgen properties that might further enhance its appeal in autism, particularly in a definable subset of hyperandrogenic autistic children. One case report is briefly reviewed demonstrating objective clinical improvements in an autistic child after spironolactone administration.

Bradstreet et al., 2006 Med Hypotheses 68(5): 979-87

Response to steroid therapy in autism secondary to autoimmune lymphoproliferative syndrome

Previously developmentally normal, he had symptoms of autism with rapid regression in developmental milestones coincident with the onset of lymphoproliferation and autoimmune hemolytic anemia. Low-dose steroid therapy induced early and complete remission in the ALPS phenotype. There was subjective improvement, followed by objective improvement in speech and developmental milestones. We propose that autism may be part of the autoimmune disease spectrum of ALPS in this child.

**Case Study: Corticosteroid Treatment of Language Regression in Pervasive Developmental Disorder**

The authors describe a child whose language and behavior regressed at 22 months and in whom pervasive developmental disorder was later diagnosed. At 6 years, he displayed a profound receptive-expressive aphasia accompanied by behavioral disturbances characterized by hyperactivity, impaired social interactions, tantrums, gestural stereotypies, and echolalia. Corticosteroid treatment resulted in amelioration of language abilities and behavior.

Stefanatos et al., 1995  J Am Acad Child Adolesc Psychiatry 34(8):1107-11

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**Pulse High-Dose Steroids as Combination Therapy with Valproic Acid in Epileptic Aphasia Patients with Pervasive Developmental Delay of Autism**

A prospective study was done with 44 children with language regression and abnormal Digitrace 24 EEG epileptiform activity in sleep. All the patients were treated with a form of Depakote or Depakene for 8 to 12 weeks and were reassessed with a 24-hour EEG before the addition of weekly bolus high-dose prednisone or methylprednisolone (10 mg/kg/wk). Results of poststeroid add-on treatment were available for 25 cases. Of these patients, EEG showed further improvement in 60% (n = 15), with no improvement seen in 40% (n = 10). Clinical speech data showed the combination of Depakote/Depakene and pulse dose steroid treatment yielding improvement in 82% (n=36). Side effects were unremarkable with no cushingoid complications even after 18 months of therapy.

Chez et al., 1998  Annals Neurology 44(3):539
Corticosteroid therapy in regressive autism: a retrospective study of effects on the Frequency Modulated Auditory Evoked Response (FMAER), language, and behavior

Methods
Twenty steroid-treated R-ASD (STAR) and 24 not-treated ASD patients (NSA), aged 3 - 5 years, were retrospectively identified from a large database. All study participants had two sequential FMAER and EEG studies; Landau-Kleffner syndrome diagnosis was excluded.

Results
The STAR group showed a significant increase in the 4 Hz FMAER spectral response and a significant reduction in response distortion compared to the NSA group. Star group subjects' language ratings were significantly improved and more STAR than NSA group subjects showed significant language improvement. Most STAR group children showed significant behavioral improvement after treatment. STAR group language and behavior improvement was retained one year after treatment. Groups did not differ in terms of minor EEG abnormalities. Steroid treatment produced no lasting morbidity.

Duffy, et al., 2014  BMC Neurology 14(1):70

In documented autistic children, 400mg/kg IVIG was administered each month for 6 months. Baseline and monthly Aberrant Behavior Checklists were completed on each child in order to measure the child’s response to IVIG. The participants’ overall aberrant behaviors decreased substantially soon after receiving their first dose of IVIG. Further analysis of the total scores revealed decreases in hyperactivity, inappropriate speech, irritability, lethargy and stereotypy. However, 22 of the 26 children regressed to their pre-IVIG status within 2–4 months of discontinuing the IVIG.


In an open-label study of 10 children with autism who also had abnormal serum immunoglobulin levels, IVIG (400 mg/kg) was given monthly for at least 6 months. No adverse effects were noted, and improvements were observed in social interaction, eye contact, speech, and response to commands; in 2 children, the improvements in speech were large, and one child “almost completely recovered speech.”


Immunoglobulins as an alternative strategy of psychopharmacological treatment of children with autistic disorder

Niederhofer, et al., 2003 Neuropsychopharmacology 28(5):1014-1015

Table 1 Improvement of ABC and Symptom Checklist Factors

<table>
<thead>
<tr>
<th>Subscale</th>
<th>Immunoglobulins</th>
<th>Placebo</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>ABC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>11.9 ± 7.2</td>
<td>14.3 ± 5.2</td>
<td>0.041*</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>19.7 ± 11.8</td>
<td>22.9 ± 11.7</td>
<td>0.036*</td>
</tr>
<tr>
<td>Inadequate eye contact</td>
<td>7.4 ± 3.6</td>
<td>8.2 ± 5.4</td>
<td>0.041*</td>
</tr>
<tr>
<td>Inappropriate speech</td>
<td>4.9 ± 3.7</td>
<td>6.4 ± 2.3</td>
<td>0.042*</td>
</tr>
<tr>
<td>Symptom checklist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3.2 ± 3.5</td>
<td>1.3 ± 2.0</td>
<td>0.020*</td>
</tr>
<tr>
<td>Decreased activity</td>
<td>4.3 ± 3.2</td>
<td>2.8 ± 3.1</td>
<td>0.034*</td>
</tr>
</tbody>
</table>

* <0.05.
Both genetic and environmental factors appear to contribute to the pathogenesis of autism. Accumulating data including changes in immune responses, linkage to major histocompatibility complex antigens, and the presence of autoantibodies to neural tissues/antigens suggest that the immune system plays an important role in its pathogenesis. In this brief review, we discuss the data regarding changes in both innate and adaptive immunity in autism and the evidence in favor of the role of the immune system, especially of maternal autoantibodies in the pathogenesis of a subset of patients with autism. The rationale for possible therapeutic use of intravenous immunoglobulin is also discussed.


Of 17 screened patients, 14 completed the trial and received IVIG treatment (1 g/kg dose) for ten 21-day treatment cycles… Significant improvements from baseline to study endpoint were observed in several subscales of the CCC-2, SRS, CGI-I, CGI-S, and ADOS, including Associated Maladaptive Behaviors (P ≤ .043), Reciprocal Social Interaction (P = .015), Communication (P < .001), and Stereotyped Behaviors and Repetitive Interests (P ≤ .013). Statistically significant reductions were also seen in numerous secondary outcomes of immunological biomarkers indicative of neuroinflammation. IVIG was well tolerated; no subjects withdrew due to an adverse event, and clinical data showed no evidence of thromboembolic events.

The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: an open-label pilot study

A trend towards improvement in mean CRP was present in both groups; the largest improvements were observed in children with initially higher elevations in CRP. When all 18 children were pooled, a significant improvement in CRP was found (p = 0.021). Pre- and post-parental observations indicated statistically significant improvements in both groups, including motivation, speech, and cognitive awareness (p < 0.05). No major adverse events were observed.

Conclusions
In this prospective pilot study of children with autism, HBOT at a maximum pressure of 1.5 atm with up to 100% oxygen was safe and well tolerated. HBOT did not appreciably worsen oxidative stress and significantly decreased inflammation as measured by CRP levels.

Rossignol et al., 2009 BMC Pediatr 7(1): 36

Hyperbaric treatment for children with autism: A multicenter, randomized, double-blind, controlled trial

After 40 sessions, mean physician CGI scores significantly improved in the treatment group compared to controls in overall functioning (p = 0.0008), receptive language (p < 0.0001), social interaction (p = 0.0473), and eye contact (p = 0.0102); 9/30 children (30%) in the treatment group were rated as "very much improved" or "much improved" compared to 2/26 (8%) of controls (p = 0.0471); 24/30 (80%) in the treatment group improved compared to 10/26 (38%) of controls (p = 0.0024). Mean parental CGI scores significantly improved in the treatment group compared to controls in overall functioning (p = 0.0336), receptive language (p = 0.0168), and eye contact (p = 0.0322). On the ABC, significant improvements were observed in the treatment group in total score, irritability, stereotypy, hyperactivity, and speech (p < 0.03 for each), but not in the control group.

Rossignol et al., 2009 BMC Pediatr 9: 21
Hyperbaric oxygen treatment for inflammatory bowel disease: A systematic review and analysis

Thirteen studies of HBOT in Crohn’s disease and 6 studies in ulcerative colitis were identified. In patients with Crohn’s disease, 31/40 (78%) had clinical improvements with HBOT, while all 39 patients with ulcerative colitis improved. One study in Crohn’s disease reported a significant decrease in proinflammatory cytokines (IL-1, IL-6 and TNF-alpha) and one study in ulcerative colitis reported a decrease in IL-6 with HBOT. Adverse events were minimal. Twelve publications reported using HBOT in animal models of experimentally-induced IBD, including several studies reporting decreased markers of inflammation or immune dysregulation, including TNF-alpha (3 studies), IL-1beta (2 studies), neopterin (1 study) and myeloperoxidase activity (5 studies). HBOT also decreased oxidative stress markers including malondialdehyde (3 studies) and plasma carbonyl content (2 studies).


Anti-inflammatory medications: Typical doses

- Prednisone: 1-2 mg/kg/day tapered unless using higher-dose protocol
- Spironolactone: 2-3 mg/kg/day
- Singulair: 4-10 mg/day
- Minocycline: 50-100 mg twice a day
- Pentoxifylline 100-400 mg twice a day
- Celecoxib: up to 300 mg per day
- IVIG: 400-800 mg/kg once a month
Immune problems in Autism and the connection between PANS and Autism

Dan Rossignol MD FAAFP

NAA Conference | May 17, 2019

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Immune Dysregulation/ Activation in Autism

NAA Conference | May 17, 2019
Infectious and immune factors in the pathogenesis of neurodevelopmental disorders: epidemiology, hypotheses, and animal models

Both genetic and environmental factors contribute to the pathogenesis of a wide variety of neurodevelopmental disorders, including autism. In other disorders with genetic influences, exogenous factors, and the timepoint(s) during nervous system development at which they are introduced, modulate expression of disease. Elucidation of the mechanisms guiding this intricate interplay between host response genes, environmental agents, and the neurodevelopmental context within which these interactions occur, is necessary to understand the continuum of clinical outcomes. This chapter will review the evidence that infectious and immune factors may contribute to the pathogenesis of neurodevelopmental disorders, describe an animal model of neurodevelopmental disorders based upon viral infection, identify processes by which neural circuitry may be compromised, and outline areas for future research.


Treatment of late onset autism as a consequence of probable autoimmune processes related to chronic bacterial infection

Two cases are described of children who at first developed normally, but before the age of three developed autistic symptoms following the reactivation of a chronic oto-rhinolaryngologic infection. The clinical and laboratory data of the cases support the aetiological hypothesis of an autoimmune process. Adrenocorticotrophic hormone (ACTH), prescribed in the first months of the disease, cured one case. The other patient, who was two years old when autistic symptoms appeared and was treated only six years later, showed a partial but definitive improvement with the immunosuppressive treatment. This report proposes that reactivation of a chronic bacterial infection be included among the aetiologies of Late Onset Autism, and demonstrates that, when the aetiological hypothesis of an autoimmune process based on clinical and laboratory data is considered, an immunosuppressive treatment, particularly with ACTH, can be very effective and also safe.

Matarazzo, 2002  World J Biol Psychiatry 3(3):162-166
Effects of the enteric bacterial product propionic acid on object-directed behavior, social behavior, cognition and neuroinflammation in adolescent rats: Relevance to autism spectrum disorder

Here we administered propionic acid (PPA), a short chain fatty acid that is used as a food preservative and also is a metabolic end-product of enteric bacteria in the gut, to adolescent (41 +/- 4 days) male rats in a study of restricted/repetitive behavior, social behavior, and cognition. The goal was to further evaluate the effects of PPA in young rodents. PPA (4 µl of 0.26 M solution) was administered intracerebroventricularly prior to each behavioral test. Rats treated with PPA displayed restricted behavioral interest to a specific object among a group of objects, impaired social behavior, and impaired reversal in a T-maze task compared to controls given phosphate buffered saline. Immunohistochemical analysis of brain tissue from PPA rats revealed reactive astrogliosis and activated microglia, indicating an innate neuroinflammatory response.

MacFabe et al., 2011 Behav Brain Res 217(1): 47-54

Enteric short-chain fatty acids: microbial messengers of metabolism, mitochondria, and mind: implications in autism spectrum disorders

Clinical observations suggest that gut and dietary factors transiently worsen and, in some cases, appear to improve behavioral symptoms in a subset of persons with autism spectrum disorders (ASDs), but the reason for this is unclear. Emerging evidence suggests ASDs are a family of systemic disorders of altered immunity, metabolism, and gene expression. Pre- or perinatal infection, hospitalization, or early antibiotic exposure, which may alter gut microbiota, have been suggested as potential risk factors for ASD. Can a common environmental agent link these disparate findings? This review outlines basic science and clinical evidence that enteric short-chain fatty acids (SCFAs), present in diet and also produced by opportunistic gut bacteria following fermentation of dietary carbohydrates, may be environmental triggers in ASD. Cont.....

MacFabe, 2015 Microb Ecol Health Dis 26:28177
Enteric short-chain fatty acids:
microbial messengers of metabolism, mitochondria, and mind: implications in autism spectrum disorders

... Of note, propionic acid, a major SCFA produced by ASD-associated gastrointestinal bacteria (clostridia, bacteroides, desulfovibrio) and also a common food preservative, can produce reversible behavioral, electrographic, neuroinflammatory, metabolic, and epigenetic changes closely resembling those found in ASD when administered to rodents. Major effects of these SCFAs may be through the alteration of mitochondrial function via the citric acid cycle and carnitine metabolism, or the epigenetic modulation of ASD-associated genes, which may be useful clinical biomarkers. It discusses the hypothesis that ASDs are produced by pre- or post-natal alterations in intestinal microbiota in sensitive sub-populations, which may have major implications in ASD cause, diagnosis, prevention, and treatment.

MacFabe, 2015 Microb Ecol Health Dis 26:28177

Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism

Considering an autoimmunity and autism connection, brain autoantibodies to myelin basic protein (anti-MBP) and neuron-axon filament protein (anti-NAFP) have been found in autistic children. In this current study, we examined associations between virus serology and autoantibody by simultaneous analysis of measles virus antibody (measles-IgG), human herpesvirus-6 antibody (HHV-6-IgG), anti-MBP, and anti-NAFP. We found that measles-IgG and HHV-6-IgG titers were moderately higher in autistic children but they did not significantly differ from normal controls. Moreover, we found that a vast majority of virus serology-positive autistic sera was also positive for brain autoantibody: (i) 90% of measles-IgG-positive autistic sera was also positive for anti-MBP; (ii) 73% of measles-IgG-positive autistic sera was also positive for anti-NAFP; (iii) 84% of HHV-6-IgG-positive autistic sera was also positive for anti-MBP; and (iv) 72% of HHV-6-IgG-positive autistic sera was also positive for anti-NAFP.

[Association between HSV-2 infection and serum anti-rat brain antibodies in patients with autism]

Growing evidence suggests that the microbiome conditions host immunity to microbes and xenobiotics, and regulates autoimmune responses that can affect the central nervous system (CNS). The presence of CNS receptors for cytokines and other immune molecules underscores the importance of brain-immune crosstalk in maintaining normal function. An increased prevalence of familial autoimmunity, exposure to pathogens prenatally and postnatally, and findings of antibrain antibodies is common in disorders as diverse as schizophrenia, obsessive-compulsive disorder and autism, and suggests that differences in exposure timing and genetic vulnerability toward autoimmunity are important determinants of neuropsychiatric outcomes.

Summary

Microbes, both pathogenic and commensal, can induce autoantibodies that bind to brain and affect behavior in susceptible hosts.


Mora, et al., 2009 Invest Clin 50(3):315-326
Viruses and autism

Search parameters for viruses and ASD

- Date of most recent search: 01/21/2019
- Sources: PubMed, Scopus, Google Scholar, references from review and other articles, database
- Excluded: review articles, letters to editor (unless new data presented)
To date, there is evidence of systemic viral infections that occur with some neurodegenerative conditions such as Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, multiple sclerosis, autism spectrum disorders, and HIV-associated neurocognitive disorders. In addition to established non-viral-induced reasons for neurodegenerative diseases, neuropathic infections and viruses associated with neurodegenerative diseases have been proposed. Neuronal degeneration can be either directly or indirectly affected by viral infection. Viruses that attack the human immune system can also affect the nervous system and interfere with classical pathways of neurodegenerative diseases. Viruses can enter the central nervous system, but the exact mechanism cannot be understood well. Various studies have supported viral- and non-viral-mediated neurodegeneration at the cellular, molecular, genomic and proteomic levels. The main focus of this review is to illustrate the association between viral infections and both neurodegenerative and neurobehavioral diseases, so that the possible mechanism and pathway of neurodegenerative diseases can be better explained.

Karim, et al., 2014 CNS Neurol Disord Drug Targets 13(7):1213-1223

A case of intrauterine cytomegalovirus infection with onset of autistic symptoms apparently after 6 months of age is reported. Physicians who find autistic symptoms in very young children might include cytomegalovirus in their differential to document the presence or absence of a correlation.

Two cases of congenital cytomegalovirus infection associated with autism are reported. The viral hypothesis of autism is discussed along with a brief review of the literature. Suggestions are made for future research.


Two children with congenital cytomegalovirus (CMV)-infection, severely disabled where autism was one of the disabilities are described. The characterization of the maternal infection have been possible and the connection between congenital CMV-infection and autism is discussed.

Ivarsson, et al., 1990  Neuropediatrics 21(2):102-103
We encountered seven children with symptomatic congenital cytomegalovirus (CMV) infection from 1988 to 1995, of whom two (28.6%) developed typical autistic disorder. Case 1: A boy born at 38 weeks' gestation with a birth weight of 3164 g showed generalized petechiae, hepatosplenomegaly, and positive serum CMV-specific IgM antibodies. He was profoundly deaf, mentally retarded, and exhibited a lack of eye contact, stereotyped repetitive play, and hyperactivity. Case 2: A boy delivered at 39 weeks gestation with a birthweight of 2912 g showed non-progressive dilation of the lateral ventricles observed postnatally. CMV-specific IgM antibodies were positive and CMV-DNA in the urine was confirmed by PCR. The boy was mentally retarded but not deaf. He showed no interest in people and delayed speech development. Subependymal cysts were detected by cranial ultrasound after birth in both patients. This is the first report describing subependymal cysts and the later development of AD. These findings suggest that the timing of injury to the developing brain by CMV may be in the third trimester in some patients with autistic disorder.


Previous research has identified a relationship between autistic disorder (autism) and specific congenital infections. Three cases of congenital or perinatal cytomegalovirus (CMV) infection occurring in association with autism are described. Hypothetical mechanisms relating congenital infection, such as CMV, to the development of autism are discussed. A better understanding of the immunologic response to certain congenital infections may provide important information pertaining to the pathophysiology and etiology of autism in vulnerable individuals.

Prevalence and titre of antibodies to cytomegalovirus and Epstein-Barr virus in patients with autism spectrum disorder

Few studies have explored the role of Cytomegalovirus (CMV) and Epstein Barr Virus (EBV) as potential etiological factors of ASD. The aim of the present study was to evaluate the seropositivity rate and antibody titre to CMV and EBV in children with ASD compared to same-aged healthy controls. Patients and Methods: We compared the seropositivity rate and titre of antibodies to CMV and EBV in 54 children with ASD (19 with autistic disorder and 35 with non-autistic disorder ASD) and in 46 controls. Results: Seropositivity rate and titre of the two antibodies were not dissimilar between cases and controls. However, considering only patients with ASD, those seropositive for CMV tended to test worse to the major severity scales than the seronegative ones. Conclusion: Titre and seropositivity rate of antibodies to CMV and EBV are similar between children with ASD and healthy controls.

Gentile, et al., 2014  In Vivo 28(4):621-626

An Italian Prospective Experience on the Association Between Congenital Cytomegalovirus Infection and Autistic Spectrum Disorder

The aim of this retrospective study, with prospective data collection, was to correlate congenital cytomegalovirus (CMV) infection with autism spectrum disorder (ASD) and to define its prevalence. Seventy proven congenitally-infected infants, born between 2007 and 2012, were referred to our centre for CMV diagnosis and follow-up, which consisted of a consolidated protocol allowing an early evaluation of autism. We considered four children 2-year old, two of whom, at the age of 3, were diagnosed with ASD demonstrating a 2-3 fold higher prevalence (2.86%), than that in general Italian population (0.66-1.36%). Our protocol enabled us to make the earliest diagnosis and highlight the role of the virus among other causes of autism, which may be a long term sequela of congenital CMV.

Acquired reversible autistic syndrome in acute encephalopathic illness in children

During an acute encephalopathic illness, a clinical picture developed in three children that was consistent with infantile autism. This development was reversible. It was differentiated from acquired epileptic aphasia, and the language disorder was differentiated aphasia. One child has rises in serum herpes simplex titers, and a computerized tomographic (CT) scan revealed an extensive lesion of the temporal lobes, predominantly on the left. The other two, with similar clinical syndromes, had normal CT scans, and no etiologic agent was defined. These cases are examples of an acquired and reversible autistic syndrome in childhood, emphasizing the clinical similarities to bilateral medial temporal lobe disease as described in man, including the Kluver-Bucy syndrome seen in postencephalitic as well as postsurgical states.


Herpes simplex virus (HSV) antibodies in child psychiatric patients and normal children

The prevalence of herpes simplex virus (HSV) antibodies has been investigated in 123 child psychiatric patients and 86 normal children. HSV antibodies were measured by ELISA technique. The prevalence of HSV antibodies in different diagnostic groups (conduct disorder, emotional disorder, hyperkinetic syndrome, anorexia nervosa, infantile autism and borderline schizophrenia in childhood) was compared with age-matched normal children, but no significant differences were found.

Onset at age 14 of a typical autistic syndrome. A case report of a girl with herpes simplex encephalitis


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The author describes a previously healthy man who contracted herpes encephalitis at the age of 31 years, and over the following months developed all the symptoms considered diagnostic of autism. This case report casts doubt on the notion of autism as an exclusively developmental disorder. It is suggested that temporal lobe damage may cause autism in some cases.

Autistic symptoms following herpes encephalitis

Autism is a childhood onset neurodevelopmental disorder characterized by reciprocal social deficits, communication impairment, and rigid ritualistic interests, with the onset almost always before three years of age. Although the etiology of the disorder is strongly influenced by genes, environmental factors are also important. In this context, several reports have described its association with known medical conditions, including infections affecting the central nervous system. In this report, we describe an 11-year-old Asian youngster who developed the symptoms of autism following an episode of herpes encephalitis. In contrast to previous similar reports, imaging studies suggested a predominant involvement of the frontal lobes. At follow-up after three years, he continued to show the core deficits of autism.

Ghaziuddin, et al., 2002  Eur Child Adolesc Psychiatry 11(3):142-146

Prevalence of herpes simplex virus 1 and 2 antibodies in patients with autism spectrum disorders

Background/Aim: The etiology of autism spectrum disorder (ASD) is unknown, even though it is hypothesized that a viral infection could trigger this disorder. The aim of this study was to evaluate the seropositivity rate and antibody level of Herpes Simplex Virus 1 (HSV1) and Herpes Simplex Virus 2 (HSV2) in children with ASD compared to same-aged healthy controls. Patients and Methods: We compared seropositivity rate and levels of antibodies to HSV1/2 in 54 children with ASD (19 with autistic disorder and 35 with non-autistic ASD) and in 46 controls. Results: Seropositivity rate and levels of anti-HSV1/2 were not dissimilar between cases and controls. Exposure to HSV2 was minimal. Conclusion: Rate of contact with HSV1 and HSV2 assessed by the mean of detection of specific antibodies was similar between children with ASD and healthy controls.

Prevalence of HHV-6 and HHV-8 antibodies in patients with autism spectrum disorders

Several viral infections have been associated with ASD etiopathogenesis but few studies have ever focused on the role of HHV-6 and HHV-8, two members of the herpesviridae family. The aim of the present study was to evaluate seropositivity rate and levels of antibodies to HHV-6 and HHV-8 in children with ASD compared to controls.

PATIENTS AND METHODS: We measured and compared seropositivity rate and levels of antibodies to HHV-6 and HHV-8 in 30 children with ASD (14 with autistic disorder and 16 with non-autistic disorder ASD) and in 28 healthy controls of the same age.

RESULTS: Seropositivity rate and levels of the two antibodies were similar in cases and controls. Seropositivity rate and levels of antibodies were not correlated with disease severity in children with ASD.

CONCLUSION: Levels and seropositivity rate of antibodies to HHV-6 and HHV-8 do not differ between children with ASD and controls.

Gentile, et al., 2013  In Vivo 27(6):843-849

Exposure to Varicella Zoster

Background/Aim: Autism spectrum disorder (ASD) is a group of central nervous system disorders lacking a definite etiology. The aim of the present study was to compare the exposure rate and titer of antibodies to Varicella Zoster Virus (VZV) in children with ASD and in healthy controls.

Patients and Methods: We enrolled 54 children with ASD and 46 control individuals.

Results: The exposure rate and titer of anti-VZV antibodies were significantly higher in children with ASD compared to controls (59% vs. 39% and 694 mIU/ml vs. 94 mIU/ml, respectively).

Conclusion: In the present case-control study, exposure to VZV was found to be independently associated with ASD.

Autistic disorder and viral infections

One proposed etiology for autism is viral infection very early in development. The mechanism, by which viral infection may lead to autism, be it through direct infection of the central nervous system (CNS), through infection elsewhere in the body acting as a trigger for disease in the CNS, through alteration of the immune response of the mother or offspring, or through a combination of these, is not yet known. Animal models in which early viral infection results in behavioral changes later in life include the influenza virus model in pregnant mice and the Borna disease virus model in newborn Lewis rats. Many studies over the years have presented evidence both for and against the association of autism with various viral infections. The best association to date has been made between congenital rubella and autism; however, members of the herpes virus family may also have a role in autism. Biological assays lend support to the association between measles virus or MMR and autism whereas epidemiologic studies show no association between MMR and autism.


Bornavirus tropism and targeted pathogenesis: virus-host interactions in a neurodevelopmental model

Animal models provide unique opportunities to explore interactions between host and environment. Two models have been established based on Bornavirus infection that provide new insights into mechanisms by which neurotropic agents and/or immune factors may impact developing or mature CNS circuitry to effect complex disturbances in movement and behavior. Distinct losses in DA pathways in the adult infection model, and the associated dramatic movement disorder that accompanies it, make it an intriguing model for tardive dyskinesia and dystonic syndromes. The neuropathologic, physiologic, and neurobehavioral features of BDV infection of neonates indicate that it not only provides a useful model for exploring the mechanisms by which viral and immune factors may damage developing neurocircuitry, but also has significant links to the range of biologic, neurostructural, locomotor, cognitive, and social deficits observed in serious neuropsychiatric illnesses such as autism.

Autism spectrum disorder secondary to enterovirus encephalitis

Millions of children are infected by enteroviruses each year, usually exhibiting only mild symptoms. Nevertheless, these viruses are also associated with severe and life-threatening infections, such as meningitis and encephalitis. We describe a 32-month-old patient with enteroviral encephalitis confirmed by polymerase chain reaction in cerebrospinal fluid, with unfavorable clinical course with marked developmental regression, autistic features, persistent stereotypes and aphasia. She experienced slow clinical improvement, with mild residual neurologic and developmental deficits at follow-up. Viral central nervous system infections in early childhood have been associated with autism spectrum disorders but the underlying mechanisms are still poorly understood. This case report is significant in presenting a case of developmental regression with autistic features and loss of language improving on follow-up.


Association of autism with polyomavirus infection in postmortem brains

Our initial step was thus to assess by nested polymerase chain reaction (PCR) and DNA sequence analysis the presence of cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus type 1 (HSV1), herpes simplex virus type 2 (HSV2), human herpes virus 6 (HHV6), BK virus (BKV), JC virus (JCV), and simian virus 40 (SV40) in genomic DNA extracted from postmortem temporocortical tissue (Brodmann areas 41/42) belonging to 15 autistic patients and 13 controls. BKV, JCV, and SV40 combined are significantly more frequent among autistic patients compared to controls (67% versus 23%, respectively; P < .05). The majority of positives yielded archetypal sequences, whereas six patients and two controls unveiled single-base pair changes in two or more sequenced clones. No association is present with the remaining viruses, which are found in relatively few individuals (N ≤ 3).

Lintas, et al., 2010  J Neurovirol 16(2):141-149
Lack of infection with XMRV or other MLV-related viruses in blood, post-mortem brains and paternal gametes of autistic individuals

Recently, the xenotropic murine leukemia virus-related virus (XMRV) has been implicated in chronic fatigue syndrome (CFS) and in prostate cancer by several, though not all studies. METHODOLOGY/PRINCIPAL FINDINGS: We assessed whether XMRV or other murine leukemia virus (MLV)-related viruses are involved in autistic disorder. Using nested PCR targeted to gag genomic sequences, we screened DNA samples from: (i) peripheral blood of 102 ASD patients and 97 controls, (ii) post-mortem brain samples of 20 ASD patients and 17 sex- and age-matched controls, (iii) semen samples of 11 fathers of ASD children, 25 infertile individuals and 7 fertile controls. No XMRV gag DNA sequences were detected, whereas peripheral blood samples of 3/97 (3.1%) controls were positive for MLV. CONCLUSIONS/SIGNIFICANCE: No MLV-related virus was detected in blood, brain, and semen samples of ASD patients or fathers.

Lintas, et al., 2011 PLoS ONE 6(2):e16609

Evidence for Mycoplasma ssp., Chlamydia pneumoniae, and human herpes virus-6 coinfections in the blood of patients with autistic spectrum disorders

We examined the blood of 48 patients from central and southern California diagnosed with autistic spectrum disorders (ASD) by using forensic polymerase chain reaction and found that a large subset (28/48 or 58.3%) of patients showed evidence of Mycoplasma ssp. infections compared with two of 45 (4.7%) age-matched control subjects (odds ratio = 13.8, P < 0.001). Because ASD patients have a high prevalence of one or more Mycoplasma ssp. and sometimes show evidence of infections with Chlamydia pneumoniae, we examined ASD patients for other infections. Also, the presence of one or more systemic infections may predispose ASD patients to other infections, so we examined the prevalence of C. pneumoniae (4/48 or 8.3% positive, odds ratio = 5.6, P < 0.01) and human herpes virus-6 (HHV-6, 14/48 or 29.2%, odds ratio = 4.5, P < 0.01) coinfections in ASD patients. Continued .........

Evidence for Mycoplasma ssp., Chlamydia pneumoniae, and human herpes virus-6 coinfections in the blood of patients with autistic spectrum disorders

We found that Mycoplasma-positive and -negative ASD patients had similar percentages of C. pneumoniae and HHV-6 infections, suggesting that such infections occur independently in ASD patients. Control subjects also had low rates of C. pneumoniae (1/48 or 2.1%) and HHV-6 (4/48 or 8.3%) infections, and there were no coinfections in control subjects. The results indicate that a large subset of ASD patients shows evidence of bacterial and/or viral infections (odds ratio = 16.5, P < 0.001). The significance of these infections in ASD is discussed in terms of appropriate treatment.


Intracellular Pathogen Infections and Immune Response in Autism

METHODS: We reviewed and collected studies concerning potential associations between intracellular pathogens like viral, bacterial, and parasite infection and the risk of ASD. RESULTS: We included 14 publications, considering bacterial and/or viral infection that demonstrated the potential to trigger ASD. Nine case-control studies were included and 5 of them reported an association between infections and ASD. One of the 2 cohorts investigated demonstrated that maternal infection increased the risk of ASD in the offspring. Three cross-sectional studies demonstrated that ASD patients presented with chronic infections and active neuroinflammatory processes. Most of the reports suggest inflammatory response as a common factor, and interleukin 6 appears to be a key-player in this process. CONCLUSION: The immune responses generated by organisms that cause perinatal maternal infection, i.e., bacteria, viruses, or parasites, have been associated with the development of autism in offspring...

Abib, et al., 2018 Neuroimmunomodulation:1-9