BIBLIOGRAPHY OF TREATMENT RECOMMENDATIONS
FOR AUTISM SPECTRUM DISORDERS
By Ashley Morgan, Parent of 6 year old son, recovered from PDD-NOS, updated 11/11/04

Intensive one-to-one therapy, biological intervention, early diagnosis and intervention the last decade have been proven to be very fruitful. Below I've outlined some resources that may be helpful in getting a broad understanding that these children are no longer hopeless. Many can make dramatic gains in functioning, attend regular schools, and some can even recover. With the exception of the very early Lovaas studies, nothing is relevant today that was published earlier than 1991. The type in purple is particularly interesting.

Recommendations by federal and local government

1) "Requirements and Guidelines For Sp. Ed. And Related Services For Children (Ages 3-5) With Disabilities" State Of Connecticut Board of Education, 1991 – States "Each program's philosophy should address the following: Parent and family participation, interagency collaboration, interdisciplinary or transdisciplinary approaches to service delivery, promotion of LRE alternatives, and developmentally and individually appropriate practices".

2) "*Report of the CT Task Force on Issues for the Education of Children with Autism"* Connecticut Dept. of Education, Spring 1998 – The 8 Components of Educational Program – Early intervention, Parent involvement, a focus on social interaction and communication, Intensive programming (5-6 hours per day plus 10-12 hours by family), Direct teaching within structured setting (ABA), Programming for generalization, Specifically-trained personnel, Planned integration with typical peers.

3) Report of the Recommendations – Autism/PDD, Assessment and Intervention For Young Children (Age 0-3 years), 1996, New York State Dept. Of Health, Early Intervention Program. Page 35. This is NY's "best practices." Stresses early intervention, 20 hour minimum of intensive one-to-one therapy for PDD/Autism spectrum disorders.

4) Preschool Education Programs for Children with Autism, 2001– A summary of 9 successful programs. All stress importance of early intervention, intensive one-to-one therapy, and parent involvement. Denver Model states "Families should be at the helm of their children's treatment", and that "Lack of progress generally signals problems with the design and implementation of the educational activity, rather than the inability of the child to learn." The Rutgers Program showed ABA to be extremely successful, with it's finding consistent with previous research done by Dr. Lovaas. **Half of their sample were placed in regular ed with no support, or with minimal support, 2 years into treatment. Over half scored in the non-autistic range on the CARS, a fifth scored above average on the Vineland.**

5) Educating Children with Autism, National Research Council, 2001 – Was charged this project after IDEA. Stresses early intervention, intensive instructional programming for a minimum of the equivalent of a full school day, (at least 25 hours), one-to-one therapy, small groups, inclusion of a family component, including parent training, etc.

Major newspaper and journal articles

6) "*Autism Therapy Is Called Effective, but Rare*", New York Times, by Laurie Tarkan 10/22/02 – States "Intensive early intervention is both effective and essential". Sites article in Behavioral Intervention, 1998**, "that if 100 children were given early intensive intervention and 40 of them had only partial improvement, the public would save $9.5 million over their school years, ages 3 to 22."**

7)"*Pivotal areas in intervention for autism",* Clinical Child Psychology, 3/01, Koegel, L. Koegel, and McNerney**. "…when children with autism are motivated to initiate complex social interactions, it may reverse a cycle of impairment, resulting in exceptionally favorable intervention outcomes for many children" in a "time and cost-effective manner".**

8) Newsletter Spring 2002, FECA (Foundation for Educating Children with Autism) – "Studies have continued to show that **intensity of hours** continues to play a major role in the success of the program".

9) "**Cost-Benefit Estimates For Early Intensive Behavioral Intervention For Young Children with Autism – General Model and Single State Case**". Jacobson, Mulick, and Green. Quoted by New York Times journalist, see above.

Intensive One-To-One Therapies

ABA is currently the most utilized therapy and proven therapy as we sit here today in 2004. Other intensive therapies that have also been proven to be effective are RDI (Relationship Development Intervention), VBA (Verbal Behavior Analysis), any many others. The research in many cases are in their infancy since a lot is still new. Also, parents are reluctant to try "just one thing", sacrificing their kid for science.

10) Lovaas has published several articles and studies about the B.F.Skinner type of therapy he founded. Here they are below followed by a summary of the research

"Behavioral Treatment and Normal Educational and Intellectual Functioning in Young Autistic Children", Ivar Lovaas, Journal of Consulting and Clinical Psychology, 1987, Vol 55, No. 1, 3-9.
Lovaas, O. I. (1987). **Behavioral treatment and normal educational and intellectual functioning in young autistic children.** Journal of Consulting and Clinical Psychology, 55, 3-9.
Lovaas, O. I. & Smith, T. (1989). **A comprehensive behavioral theory of autistic children: Paradigm for research and treatment.** Journal of Behavioral Therapy and Experimental Psychiatry, 20, 17-29.
McEachin, J. J., Smith, T., & Lovaas, O. I. (1993). **Long-term outcome for children with autism who received early intensive behavioral treatment.** American Journal on Mental Retardation, 97 (4), 359-372. (See also the commentaries on this study)

A Brief Review of Key Empirical Studies in ABA

Thirty years of research demonstrated the efficacy of applied behavioral methods in reducing inappropriate behavior and in increasing communication, learning, and appropriate social behavior. A well-designed study of a psychosocial intervention was carried out by Loovas and colleagues (Lovaas, 1987; McEachin et al., 1993). Nineteen children with autism were treated intensively with behavior therapy for 2 years and compared with two control groups.

Follow-up of the experimental group in first grade, in late childhood, and in adolescence found that nearly half the experimental group but almost none of the children in the matched control group were able to participate in regular schooling. Up to this point, a number of other research groups have provided at least a partial replication of the Lovaas model (see Rogers, 1998).

Lovaas, O.I. (1987). Behavior treatment and normal educational and intellectual functioning in young autistic children. Journal of Consulting and Clinical Psychology, 55, 3-9.

In this study, Lovaas compared three groups of young autistic children. The experimental group consisted of 19 children all of whom received approximately 40 hours per week of behavioral intervention from the staff of the Young Autism Project. The first control group also consisted of 19 autistic children, however, these children only received an average of 10 hours of 1:1 behavioral intervention per week from the staff of the Young Autism Project. The second control group received a similar level of intervention as control group 1, however, they were treated by an outside provider.
Results indicated that the children receiving intensive 1:1 behavioral intervention did substantially better than those children only receiving 10 hours per week or less of intervention.
Specifically, 47% of the experimental group achieved normal intellectual functioning and were placed in mainstream classrooms without assistance, 40% were placed in language impaired classrooms and were mildly mentally retarded, and only 10% were placed in classrooms for autistic and profoundly retarded children following the treatment.
In contrast, only 2% of control subjects (1 and 2) achieved normal intellectual functioning with mainstreamed placement, while 45% were found to be in the mildly retarded language impaired classes, and 53% were placed in autistic / severely mentally handicapped classrooms following treatment.

Experimental Group	**Control Group 1**	**Control Group 2**
Tx = 40 hrs/week Young Autism Project	Tx = 10 hrs/week Young Autism Project	Tx = 10 hrs/week Outside provider
Recovery: N = 9	Recovery: N = 0	Recovery: N = 1
Aphasic: N = 8	Aphasic: N = 8	Aphasic: N = 10
Autistic / MR: N = 2	Autistic / MR: N = 11	Autistic / MR: N = 10
N(total) = 19	N(total) = 19	N(total)= 21

Results indicate that both the method of treatment and the intensity of treatment are critical factors in positive outcome for young children diagnosed with autism.

McEachin, J.J., Smith, T. & Lovaas, O.I. (1993). Long-term outcome for children with autism who received early intensive behavioral treatment. American Journal on Mental Retardation, 97, 359-372.

McEachin et al. (1993) questioned whether the substantial gains reported in the subjects of the Lovaas study (1987) were prolonged years after the treatment was terminated.
Results indicate that of the **47% of the experimental subjects who had achieved normal intellectual and educational functioning**, 88% (or 8 out of 9 subjects) had maintained the gains approximately 6 years after treatment (mean age = 11.5).
In addition, experimental subjects were found to have substantially higher adaptive functioning ratings than the original control group. Results show that the positive effects of intensive behavioral intervention are substantial and long lasting.

Here is what an ABA program can look like for many children, as each kid is different. FYI this chart is what a company CARD (Center For Autism and Related Disorders) uses as their curriculum.

	Services	**Skills Taught**
YEAR ONE	40 hours of 1:1 in-home behavioral intervention.	Simple compliance, self-help, motor imitation, receptive and expressive object and action labeling, simple requests, and basic toy manipulation.
YEAR TWO	5-10 hours of preschool with a CARD shadow targeting social skills, and 30-35 hours of 1:1 in-home behavioral intervention.	Complex skills including imaginary play, describing and complex language, emotion recognition, and basic cause and effect, with an emphasis on generalization.
YEAR THREE	15 hours of general-education Kindergarten with a CARD shadow, targeting attention, classroom behavior, academics, and social development, and 20 hours of 1:1 in-home behavioral intervention.	Abstract skills such as abstract reasoning, senses, observational learning, and social skills are targeted.
YEAR FOUR	30 hours of attendance in general education First Grade, and 10-15 hours of in-home therapy.	The final treatment year should focus entirely on social skills and academic achievement in first grade. Typically, theory of mind and executive functioning skills, understanding cause and effect relationships, and comprehending social cues are the primary focus. In addition, parent and teacher training is completed so that treatment gains may be maintained after therapy is terminated.

Recovery Article by Founder of Autism Research Institute

Autism Research Review International, 1994, Vol. 8, No. 2, page 3

Recovery from autism is possible

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Autism. The word seems synonymous with controversy. There is hardly a statement that can be made about autism that has not been challenged. The most recent controversy concerns the concept of recovery. Conventional wisdom has held, from the very beginning, that autism is a life-long disability and that, while some individuals may improve, autism is always there.

Conventional wisdom notwithstanding, we are beginning to hear increasingly about recovery. The matter deserves our close attention. Reports of recovery, partial recovery, or near-recovery, come from several sources:

Mysterious spontaneous recovery. It hasn't happened often, but it has happened often enough for the phenomenon to be worth noting: over the past 25 years I have received a handful of letters from parents which read something like this: "Please remove our address from your files. Our child has continued to improve so greatly—we don't know why—that now he is no longer considered autistic. We think it best that he never even find out that he was considered autistic, so we don't want any mail coming into our home with the word `autism' on it ...." In a few of these cases we have received follow- up letters, years later, telling us that the formerly autistic child has now graduated from high school, or college, or has gotten married, but "please don't write to acknowledge this letter."

Personal accounts. In recent years there have appeared a number of books authored by autistic persons who have recovered significantly, if not completely. Temple Grandin, whose book *Emergence: Labeled Autistic* (1986) has elevated her to celebrity status, has earned a Ph.D. in animal science. She lectures extensively as an expert on both cattle handling procedures and autism. While she is an independent and respected professional, she acknowledges that her recovery from autism is not complete.

Donna Williams' story of partial recovery from autism is told in her two books *Nobody Nowhere* (1992), and *Somebody Somewhere* (1994). Like Temple Grandin, Donna's writings have earned her celebrity status. She has appeared on national television in both the U.S. and the U.K. Like Temple, she acknowledges—and is handicapped by—many symptoms of autism. Like Temple, she forges gallantly ahead, accomplishing more with her life than most "non-handicapped" people can hope to achieve.

Mother-child accounts. Several mothers have written chronicles of the recoveries of their autistic sons, with chapters or afterwords written by the sons themselves. In *Face to Face* (1986) Lurline Morphett describes her son Simon, at 24, as a "whole person to whom the label of autism is entirely inappropriate." Simon, in his chapter, refers to himself as "a [formerly] hopeless kid recovering to become quite normal."

In *Fighting for Tony* (1987), Mary Callahan tells how taking Tony off milk transformed him from autistic to normal (see ARRI 3/2). Now, seven years later, he is a very normal teenager.

Judging from *There's a Boy in Here,* the book Sean Barron co-authored with his mother Judy Barron (1992), Sean also seems to have left autism behind him. In closing his mother writes, "... now he has begun giving us advice on our problems—good advice." She refers to his "successful struggle against autism."

Annabel Stehli's widely-known book *The Sound of a Miracle* (1991) tells of her daughter Georgie's speedy recovery after treatment with Auditory Integration Training (AIT). A TV "docudrama" is underway.

Jane McDonnell's book *News From the Border* (1993) includes an afterword by her son Paul, in which he says, "I am not as autistic as I was, but autism still shows in certain ways." But the ways are minor, and judging from both the book and the McDonnell's appearance on the *Sonya Live* television show, Paul has come a very long way from his autism. (Like Sean Barron, Paul McDonnell studied autistic behavior on films, e.g. *Rain Man,* and television, in order to learn what behaviors needed to be abandoned in his quest for normality.)

As you may surmise from its title, the newly published book *Autism: From Tragedy to Triumph* (1994), by Carol Johnson and Julia Crowder, also reports a dramatic success story. Here again is an afterword, written by Drew, the formerly autistic young man. The afterword is, in actuality, a biographical essay written by Drew for a second-year psychology class. He does not mention autism nor ever having been autistic. In a recent phone call from his mother, I learned that Drew is now considered normal in all respects. He has normal friendships and seems to be leading a very normal life.

What is particularly interesting about Drew is that he was one of the autistic patients enrolled in Ivar Lovaas' Young Autism Program at UCLA in the 1970s. The book includes log entries from the therapy sessions at UCLA.

The Young Autism Project. Much of the current controversy on recovery began in 1987 with publication by Ivar Lovaas and his colleagues of the results of their intensive early intervention program, starting with children under 4 years of age, which resulted in 47% of the children being successfully mainstreamed. Lovaas was quoted in a *New York Times* interview as saying, "If you met them now that they are teenagers, you would never know that anything had been wrong with them." Similar results have been reported for children entering the Princeton Child Development Institute program before the age of 5 by Fenske, Zalenski, Krantz, and McClannahan, in 1985. A later followup study of the subjects in the Lovaas study, by McEachin et al. (1993) in which peer ratings, interviews and other assessment techniques were used, supported the earlier findings that these children were indistinguishable from their peers.

Let Me Hear Your Voice. The controversy became much more clearly focused with the publication in 1993 of the book *Let Me Hear Your Voice* by Catherine Maurice, in which the author describes how her two autistic children, both diagnosed as severely autistic by noted psychologists, psychiatrists and neurologists in New York City, were brought to what appears to be complete recovery by the very intensive application of early intervention techniques, particularly the Lovaas behavioral program. Catherine Maurice includes extensive recent quotations from the children's teachers and speech-language pathologists which depict children who are not only functioning normally, but exceptionally well.

Those who don't believe recovery from autism is possible usually argue that the diagnosis must have been faulty—it wasn't autism to begin with. Since *Let Me Hear Your Voice* depicts the children's severe autism so clearly and graphically, and since the documentation of their diagnosis by expert after expert is so incontrovertible, the conclusion that these children have in fact recovered is especially hard for many to accept. I have personally seen the Maurice children on several occasions, most recently just a week or two before this writing. I can say without qualification that these children are in fact doing beautifully. They are great kids, with no sign whatever of autism.

A psychologist, a psychiatrist, and a pediatric neurologist who were among the specialists who had diagnosed the Maurice children as autistic initially have written a paper, soon to be published, indicating that the "children show no residua of autism."

What are we to make of all this?

There will, of course, always be those who persist in saying that recovery from autism is impossible (after all, autism is, by definition, a life-long disability) and that the supposed recovery of the many individuals described above must therefore be only illusory. But as a great philosopher once observed: "If it looks like a duck, walks like a duck, and quacks like a duck, it must be a duck." So say I for the concept of recovery in autism: if they *look* recovered, if they *act* recovered, and if they are thought *to be* recovered, they *are* recovered. Perhaps some of these "recovered" individuals may have some quirks and odd behaviors. If so, so what? Who doesn't?

I am more than willing to accept, and to celebrate, recovery from autism. Let's have more of it!

GI/Immune Research

Current research shows that 98% of children on the spectrum have GI and Immune irregularities. 48% of these kids show marked improvement in concentration, speech, reduction of perseverative behaviors, among others, when they implement the DAN! Protocol. DAN is a group of pediatricians that specialize in ASD kids, and do research collectively.

Journal articles regarding autism, food allergy, gastrointestinal abnormalities, gluten, dairy, and the effects of the opiate properties of milk and wheat-derived peptides on neurological function

Summary: Based on reports from caregivers, case studies, and observation of patients with schizophrenia and children with severe behavioral disorders, Dr. FC Dohan hypothesized, in 1960s and 70s, that gluten and dairy foods might worsen these behaviors. He noted that in many cases, a restricted diet could lead to significant improvement or recovery from these disorders. For several years, the biochemical explanation for this phenomenon remained unclear. However, several other studies seemed to bear out this observation, and in 1981, using more advanced laboratory technology, Dr. Karl Reichelt, Director of Clinical Chemistry for the Department of Pediatric Research at the Rikshospitalet (National Hospital) in Oslo, Norway, found and reported abnormal peptides in the urine of schizophrenics and autistics. Peptides are pieces of proteins that are not completely broken down into individual amino acids. Dr. Reichelt has observed that these peptides, which are 4 or 5 or 6 amino acids long, have sequences that match those of opioid peptides (casomorphin and gliadomorphin). The known dietary sources of these opiate peptides are casein (from milk) and gliadin or gluten (from cereal grains). He has since conducted several studies examining this finding, as have several other researchers, including Paul Shattock at the University of Sunderland in England, Dr. Robert Cade at the University of Florida, Gainesville, and Dr. Alan Friedman, of Johnson and Johnson Ortho Clinical Diagnostics. The best evidence for this correlation lies in the thousands of case reports of improvement or recovery of children with autism on this diet. However, responsible physicians who have taken the time to review these studies must agree that there is, indeed, significant scientific evidence to support a trial period of careful elimination of these proteins from the diet of children on the autistic spectrum.

White JF.: Intestinal pathophysiology in autism. Exp Biol Med (Maywood). 2003 Jun;228(6):639-49.

Summary:
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Autism is a life-long developmental disorder affecting as many as 1 in 500 children. The causes for this profound disorder are largely unknown. Recent research has uncovered pathology in the gastrointestinal tract of autistic children. The pathology, reported to extend from the esophagus to the colon, is described here along with other studies pointing to a connection between diet and the severity of symptoms expressed in autism. The evidence that there is impaired intestinal permeability in autism is reviewed, and various theories are discussed by which a leaky gut could develop. Lastly, some possible ways in which impaired gastrointestinal function might influence brain function are discussed. FULL TEXT ARTICLE at http://www.ebmonline.org/cgi/content/full/228/6/639 **Vojdani A, Pangborn JB, Vojdani E, Cooper EL.**, Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. Int J Immunopathol Pharmacol. 2003 Sep-Dec;16(3):189-99. **Summary:**

Lab. Comparative Immunology, Dept. Neurobiology, UCLA Medical Center, Los Angeles, CA, USA.

Similar to many complex autoimmune diseases, genetic and environmental factors including diet, infection and xenobiotics play a critical role in the development of autism. In this study, we postulated that infectious agent antigens such as streptokinase, dietary peptides (gliadin and casein) and ethyl mercury (xenobiotic) bind to different lymphocyte receptors and tissue enzyme (DPP IV or CD26). We assessed this hypothesis first by measuring IgG, IgM and IgA antibodies against CD26, CD69, streptokinase (SK), gliadin and casein peptides and against ethyl mercury bound to human serum albumin in patients with autism. A significant percentage of children with autism developed anti-SK, anti-gliadin and casein peptides and anti-ethyl mercury antibodies, concomitant with the appearance of anti-CD26 and anti-CD69 autoantibodies. These antibodies are synthesized as a result of SK, gliadin, casein and ethyl mercury binding to CD26 and CD69, indicating that they are specific. Immune absorption demonstrated that only specific antigens, like CD26, were capable of significantly reducing serum anti-CD26 levels. However, for direct demonstration of SK, gliadin, casein and ethyl mercury to CD26 or CD69, microtiter wells were coated with CD26 or CD69 alone or in combination with SK, gliadin, casein or ethyl mercury and then reacted with enzyme labeled rabbit anti-CD26 or anti-CD69. Adding these molecules to CD26 or CD69 resulted in 28-86% inhibition of CD26 or CD69 binding to anti-CD26 or anti-CD69 antibodies. The highest % binding of these antigens or peptides to CD26 or CD69 was attributed to SK and the lowest to casein peptides. We, therefore, propose that bacterial antigens (SK), dietary peptides (gliadin, casein) and Thimerosal (ethyl mercury) in individuals with pre-disposing HLA molecules, bind to CD26 or CD69 and induce antibodies against these molecules. In conclusion, this study is apparently the first to demonstrate that dietary peptides, bacterial toxins and xenobiotics bind to lymphocyte receptors and/or tissue enzymes, resulting in autoimmune reaction in children with autism.
Bull G, Shattock P, Whiteley P, Anderson R, Groundwater PW, Lough JW, Lees G.: Indolyl-3-acryloylglycine (IAG) is a putative diagnostic urinary marker for autism spectrum disorders. Med Sci Monit. 2003 Oct;9(10):CR422-5.

Abstract:

Sunderland General Hospital, Sunderland, UK.

BACKGROUND: Autism is a heterogeneous pervasive developmental disorder with a poorly defined aetiology and pathophysiology. There are indications that the incidence of the disease is rising but still no definitive diagnostic biochemical markers have been isolated. Here we have addressed the hypothesis that urinary levels of trans -indolyl-3-acryloylglycine (IAG) are abnormal in patients diagnosed with autism spectrum disorders (ASD) compared to age-matched controls. MATERIAL/METHODS: Urine samples were collected on an opportunistic basis and analysed for IAG concentration (normalised against creatinine content to account for changes in urinary volume) using reversed phase HPLC with UV detection. RESULTS: Statistical analysis (Mann-Whitney tests) showed highly significant increases (p=0.0002) in the levels of urinary IAG in the ASD group (median 942 microV per mmol/L of creatinine [interquartile range 521-1729], n=22) compared to asymptomatic controls (331 [163-456], n=18). Detailed retrospective analysis showed that gender (boys 625 microV per mmol/L of creatinine [294-1133], n=29; girls 460 [282-1193], n=11: P=0.79) and age (control donor median 10 years [8-14], n=15; ASD median 9 years [7-11] n=22: P=0.54) were not significantly correlated with IAG levels in this non-blinded volunteer study. CONCLUSIONS: Our results strongly suggest that urinary titres of IAG may constitute an objective diagnostic indicator for ASD. Mechanisms for the involvement of IAG in ASD are discussed together with future strategies to address its specificity.

Reichelt KL, Knivsberg AM.: Can the pathophysiology of autism be explained by the nature of the discovered urine peptides? Nutr Neurosci. 2003 Feb;6(1):19-28.

Abstract: Institute of Pediatric Research, Univ of Oslo, Rikshospitalet, N-0027, Oslo, Norway. k.l.reichelt@klinmed.uio.no

Opioid peptides derived from food proteins (exorphins) have been found in urine of autistic patients. Based on the work of several groups, we try to show that exorphins and serotonin uptake stimulating factors may explain many of the signs and symptoms seen in autistic disorders. The individual symptoms ought to be explainable by the properties and behavioural effects of the found peptides. The data presented form the basis of an autism model, where we suggest that exorphins and serotonin uptake modulators are key mediators for the development of autism. This may be due to a genetically based peptidase deficiency in at least two or more peptidases and, or of peptidase regulating proteins made manifest by a dietary overload of exorphin precursors such as by increased gut uptake.
Buie T, Winter H, Kushak, R: Preliminary findings in gastrointestinal investigation of autistic patients. 2002.

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Summary:

Harvard University and Mass General Hospital, http://www.ladders.org/autism.php

111 patients evaluated, ages 14 Months to 20 Years, all with GI symptoms of pain or diarrhea. Endoscopic findings: Esophagitis in 23 (20%), Gastritis in 14 (12%); 4 had Helicobacter pylori; Duodenitis in 11 (10%); 2 had Celiac Sprue; Eosinophilic Inflammation in 5 (5%). 10 out of 90 tested (11%) had unusually low enzyme activity: 2 with total pancreatic insufficiency and 5 with multiple enzyme defects. Lactase deficiency was found in 55% of ASD children tested, and combined deficiency of disacchraridase enzymes was found in 15%. Enzyme assays correlate well with hydrogen breath tests. Colitis was found in 11 of 89 patients (12%), none with features of Ulcerative Colitis or Crohn's. Histologic (biopsy reviewed) lymphoid nodular hyperplasia was found in 15 of 89 patients (16%). Eosinophilic inflammation was found in 13 of 89 patients (14%); cause or significance is unclear. Conclusions: more than 50% of autistic children appear to have GI symptoms, food allergies, and maldigestion or malabsorption issues. We need large, evidence-based studies need to be done in order to fully understand the gut-brain association in autism.

Krigsman, A, et al: Preliminary data presented at congressional hearing. 2002 Jun.

Summary:

New York University School of Medicine: www.med.nyu.edu

We examined 43 patients with autism, in whom we demonstrated enterocolitis in 65% and terminal ileal LNH in 90%. As of November, 2002, our total patient population now stands at 82, and the percentages of enterocolitis and LNH are essentially unchanged. Additional studies will follow.

Whiteley P, Shattock P: Biochemical aspects in autism spectrum disorders: updating the opioid-excess theory and presenting new opportunities for biomedical intervention. Expert Opin Ther Targets. 2002 Apr;6(2):175-83.

Abstract:

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Autism is a lifelong condition usually described as affecting social, cognitive and imaginative abilities. For many years, parents and some professionals have observed that in concordance with the behavioural and psychological symptoms of the condition, there are a number of physiological and biochemical correlates which may also be of relevance to the syndrome. One area of interest that encompasses many of these observations is the opioid-excess theory of autism. The main premise of this theory is that autism is the result of a metabolic disorder. Peptides with opioid activity derived from dietary sources, in particular foods that contain gluten and casein, pass through an abnormally permeable intestinal membrane and enter the central nervous system (CNS) to exert an effect on neurotransmission, as well as producing other physiologically-based symptoms. Numerous parents and professionals worldwide have found that removal of these exogenously derived compounds through exclusion diets can produce some amelioration in autistic and related behaviours. There is a surprisingly long history of research accompanying these ideas. The aim of this paper is to review the accompanying evidence in support of this theory and present new directions of intervention as a result of it.

Vojdani A, Campbell AW, Anyanwu E, Kashanian A, Bock K, Vojdani E: Antibodies to neuron-specific antigens in children with autism: possible cross-reaction with encephalitogenic proteins from milk, Chlamydia pneumoniae and Streptococcus group A. J Neuroimmunol 2002 Aug;129(1-2):168-77.

Abstract:

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We measured autoantibodies against nine different neuron-specific antigens and three cross-reactive peptides in the sera of autistic subjects and healthy controls by means of enzyme-linked immunosorbent assay (ELISA) testing. The antigens were myelin basic protein (MBP), myelin-associated glycoprotein (MAG), ganglioside (GM1), sulfatide (SULF), chondroitin sulfate (CONSO4), myelin oligodendrocyte glycoprotein (MOG), alpha,beta-crystallin (alpha,beta-CRYS), neurofilament proteins (NAFP), tubulin and three cross-reactive peptides, Chlamydia pneumoniae (CPP), streptococcal M protein (STM6P) and milk butyrophilin (BTN). Autistic children showed the highest levels of IgG, IgM and IgA antibodies against all neurologic antigens as well as the three cross-reactive peptides. These antibodies are specific because immune absorption demonstrated that only neuron-specific antigens or their cross-reactive epitopes could significantly reduce antibody levels. These antibodies may have been synthesized as a result of an alteration in the blood-brain barrier. This barrier promotes access of preexisting T-cells and central nervous system antigens to immunocompetent cells, which may start a vicious cycle. These results suggest a mechanism by which bacterial infections and milk antigens may modulate autoimmune responses in autism.

Knivsberg AM, Reichelt KL, Hoien T, Nodland M: A randomised, controlled study of dietary intervention in autistic syndromes. Nutr Neurosci 2002 Sep;5(4):251-61.

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Abstract:

Impaired social interaction, communication and imaginative skills characterize autistic syndromes. In these syndromes urinary peptide abnormalities, derived from gluten, gliadin, and casein, are reported. They reflect processes with opioid effect. The aim of this single blind study was to evaluate effect of gluten and casein-free diet for children with autistic syndromes and urinary peptide abnormalities. A randomly selected diet and control group with 10 children in each group participated. Observations and tests were done before and after a period of 1 year. The development for the group of children on diet was significantly better than for the controls.

Kidd PM.: Autism, an extreme challenge to integrative medicine. Part: 1: The knowledge base. Altern Med Rev. 2002 Aug;7(4):292-316.

Abstract:

Autism, archetype of the autistic spectrum disorders (ASD), is a neurodevelopmental disorder characterized by socially aloof behavior and impairment of language and social interaction. Its prevalence has surged in recent years. Advanced functional brain imaging has confirmed pervasive neurologic involvement. Parent involvement in autism management has accelerated understanding and treatment. Often accompanied by epilepsy, cognitive deficits, or other neurologic impairment, autism manifests in the first three years of life and persists into adulthood. Its etiopathology is poorly defined but likely multifactorial with heritability playing a major role. Prenatal toxic exposures (teratogens) are consistent with autism spectrum symptomatology. Frequent vaccinations with live virus and toxic mercurial content (thimerosal) are a plausible etiologic factor. Autistic children frequently have abnormalities of sulfoxidation and sulfation that compromise liver detoxification, which may contribute to the high body burden of xenobiotics frequently found. Frequent copper-zinc imbalance implies metallothionein impairment that could compound the negative impact of sulfur metabolism impairments on detoxification and on intestinal lining integrity. Intestinal hyperpermeability manifests in autistic children as dysbiosis, food intolerances, and exorphin (opioid) intoxication, most frequently from casein and gluten. Immune system abnormalities encompass derangement of antibody production, skewing of T cell subsets, aberrant cytokine profiles, and other impairments consistent with chronic inflammation and autoimmunity. Coagulation abnormalities have been reported. Part 2 of this review will attempt to consolidate progress in integrative management of autism, aimed at improving independence and lifespan for people with the disorder. **Kidd PM.:** Autism, an extreme challenge to integrative medicine. Part 2: medical management. Altern Med Rev. 2002 Dec;7(6):472-99. **Abstract:**

Autism and allied autistic spectrum disorders (ASD) present myriad behavioral, clinical, and biochemical abnormalities. Parental participation, advanced testing protocols, and eclectic treatment strategies have driven progress toward cure. Behavioral modification and structured education are beneficial but insufficient. Dietary restrictions, including removal of milk and other casein dairy products, wheat and other gluten sources, sugar, chocolate, preservatives, and food coloring are beneficial and prerequisite to benefit from other interventions. Individualized IgG or IgE testing can identify other troublesome foods but not non-immune mediated food sensitivities. Gastrointestinal improvement rests on controlling Candida and other parasites, and using probiotic bacteria and nutrients to correct dysbiosis and decrease gut permeability. Detoxification of mercury and other heavy metals by DMSA/DMPS chelation can have marked benefit. Documented sulfoxidation-sulfation inadequacies call for sulfur-sulfhydryl repletion and other liver p450 support. Many nutrient supplements are beneficial and well tolerated, including dimethylglycine (DMG) and a combination of pyridoxine (vitamin B6) and magnesium, both of which benefit roughly half of ASD cases. Vitamins A, B3, C, and folic acid; the minerals calcium and zinc; cod liver oil; and digestive enzymes, all offer benefit. Secretin, a triggering factor for digestion, is presently under investigation. Immune therapies (pentoxifyllin, intravenous immunoglobulin, transfer factor, and colostrum) benefit selected cases. Long-chain omega-3 fatty acids offer great promise. Current pharmaceuticals fail to benefit the primary symptoms and can have marked adverse effects. Individualized, in-depth clinical and laboratory assessments and integrative parent-physician-scientist cooperation are the keys to successful ASD management.
Hadjivassiliou M, Grunewald RA, Davies-Jones GA: Gluten sensitivity as a neurological illness. J Neurol Neurosurg Psychiatry. 2002 May;72(5):560-3. [No abstract available]

Hadjivassiliou M, Boscolo S, Davies-Jones GA, Grunewald RA, Not T, Sanders DS, Simpson JE, Tongiorgi E, Williamson CA, Woodroofe NM: The humoral response in the pathogenesis of gluten ataxia. Neurology 2002 Apr 23;58(8):1221-6.

Abstract:

Department of Clinical Neurology, The Royal Hallamshire Hospital, Sheffield, UK. m.hadjivassiliou@sheffield.ac.uk

OBJECTIVE: To characterize humoral response to cerebellum in patients with gluten ataxia. BACKGROUND: Gluten ataxia is a common neurologic manifestation of gluten sensitivity. METHODS: The authors assessed the reactivity of sera from patients with gluten ataxia (13), newly diagnosed patients with celiac disease without neurologic dysfunction (24), patients with other causes of cerebellar degeneration (11), and healthy control subjects (17) using indirect immunocytochemistry on human cerebellar and rat CNS tissue. Cross-reactivity of a commercial IgG antigliadin antibody with human cerebellar tissue also was studied. RESULTS: Sera from 12 of 13 patients with gluten ataxia stained Purkinje cells strongly. Less intense staining was seen in some but not all sera from patients with newly diagnosed celiac disease without neurologic dysfunction. At high dilutions (1:800) staining was seen only with sera from patients with gluten ataxia but not in control subjects. Sera from patients with gluten ataxia also stained some brainstem and cortical neurons in rat CNS tissue. Commercial anti-gliadin antibody stained human Purkinje cells in a similar manner. Adsorption of the antigliadin antibodies using crude gliadin abolished the staining in patients with celiac disease without neurologic dysfunction, but not in those with gluten ataxia. CONCLUSIONS: Patients with gluten ataxia have antibodies against Purkinje cells. Antigliadin antibodies cross-react with epitopes on Purkinje cells.

Garvey J: Diet in autism and associated disorders. J Fam Health Care 2002;12(2):34-8.

Abstract:

Royal Free Hospital, London.

A dietitian discusses the theory that peptides with opioid activity may cause or trigger autism. The use of an exclusion diet to treat autism is explained, weighing the potential benefits against some of the practical difficulties of keeping to a strict exclusion diet. The use of nutritional supplements is described. An abnormal gut flora has also been implicated in autism and the use of probiotics and prebiotics in improving the integrity of the gut mucosa is also discussed.

Cornish E: Gluten and casein free diets in autism: a study of the effects on food choice and nutrition. J Hum Nutr Diet 2002 Aug;15(4):261-9.

Abstract:

Senior Community Dietitian, Community Nutrition Service, South Derbyshire Community Health NHS Trust, Dar es Salaam, Tanzania.

BACKGROUND: There is growing interest in possible dietary involvement in the aetiology and treatment of Autistic Spectrum Disorders (ASD). Research has focused on the physiological and behavioural effects of dietary change but has not examined the effect of exclusion diets on nutritional intake. AIMS: The aim of this study was to examine whether the removal of major dietary staples placed children with autism at risk of nutrient deficiency and compares their food choice with ASD children not following gluten and/or casein free diets. METHODS: A postal questionnaire was sent to parents of children aged 3-16 years, diagnosed with ASD belonging to the National Autistic Society in Leicestershire and southern Derbyshire. Detailed dietary information and a 3-day food diary were collected. The sample size was small: those using gluten/casein free diets (n = 8) and those not following diet (n = 29). RESULTS: Nutrient intakes fell below the Lower Reference Nutrient Intake (LRNI) in 12 children (32%) for zinc, calcium, iron, vitamin A, vitamin B12 and riboflavin in the nondiet group and four children (50%) for zinc and calcium in the diet group. Fruit and vegetable intakes were higher and cereal, bread and potato consumption were lower in those children using gluten and/or casein free diets. CONCLUSION: No significant differences in the energy, protein and micronutrient intakes were found between the two groups of children. A longitudinal prospective study is suggested to examine whether differences in food choice are the result of dietary intervention or the prerequisite for the successful application of diet in this special group of children.

Wakefield AJ, Puleston JM, Montgomery SM, Anthony A, O'Leary JJ, Murch SH: Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. Aliment Pharmacol Ther. 2002 Apr;16(4):663-74.

Inflammatory Bowel Disease Study Group, Centre for Gastroenterology, Department of Medicine, Royal Free and University College Medical School, London, UK. wakers@aol.com

There is growing awareness that primary gastrointestinal pathology may play an important role in the inception and clinical expression of some childhood developmental disorders, including autism. In addition to frequent gastrointestinal symptoms, children with autism often manifest complex biochemical and immunological abnormalities. The gut-brain axis is central to certain encephalopathies of extra-cranial origin, hepatic encephalopathy being the best characterized. Commonalities in the clinical characteristics of hepatic encephalopathy and a form of autism associated with developmental regression in an apparently previously normal child, accompanied by immune-mediated gastrointestinal pathology, have led to the proposal that there may be analogous mechanisms of toxic encephalopathy in patients with liver failure and some children with autism. Aberrations in opioid biochemistry are common to these two conditions, and there is evidence that opioid peptides may mediate certain aspects of the respective syndromes. The generation of plausible and testable hypotheses in this area may help to identify new treatment options in encephalopathies of extra-cranial origin. Therapeutic targets for this autistic phenotype may include: modification of diet and entero-colonic microbial milieu in order to reduce toxin substrates, improve nutritional status and modify mucosal immunity; anti-inflammatory/immunomodulatory therapy; and specific treatment of dysmotility, focusing, for example, on the pharmacology of local opioid activity in the gut.

Knivsberg AM, Reichelt KL, Nodland M: Reports on dietary intervention in autistic disorders. Nutr Neurosci 2001;4(1):25-37.

Center for Reading Research, Stavanger College, Norway. ann-mari.knivsberg@slf.his.no

Abstract:

Autism is a developmental disorder for which no cure currently exists. Gluten and/or casein free diet has been implemented to reduce autistic behaviour, in addition to special education, since early in the eighties. Over the last twelve years various studies on this dietary intervention have been published in addition to anecdotal, parental reports. The scientific studies include both groups of participants as well as single cases, and beneficial results are reported in all, but one study. While some studies are based on urinary peptide abnormalities, others are not. The reported results are, however, more or less identical; reduction of autistic behaviour, increased social and communicative skills, and reappearance of autistic traits after the diet has been broken.

Jyonouchi H, Sun S, Le H.: Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression. J Neuroimmunol 2001 Nov 1;120(1-2):170-9

Abstract:
Department of Pediatrics, University ofMinnesota, MMC 610 FUMC, 420 Delaware Street SE, Minneapolis, MN55455, USA. jyono001@tc.umn.edu

We determined innate and adaptive immune responses in children with developmental regression and autism spectrum disorders (ASD, N=71), developmentally normal siblings (N=23), and controls (N=17). With lipopolysaccharide (LPS), a stimulant for innate immunity, peripheral blood mononuclear cells (PBMCs) from 59/71 (83.1%) ASD patients produced >2 SD above the control mean (CM) values of TNF-alpha, IL-1beta, and/or IL-6 produced by control PBMCs. ASD PBMCs produced higher levels of proinflammatory/counter-regulatory cytokines without stimuli than controls. With stimulants of phytohemagglutinin (PHA), tetanus, IL-12p70, and IL-18, PBMCs from 47.9% to 60% of ASD patients produced >2 SD above the CM values of TNF-alpha depending on stimulants. Our results indicate excessive innate immune responses in a number of ASD children that may be most evident in TNF-alpha production.

Hadjivassiliou M, Grunewald RA, Lawden M, Davies-Jones GA, Powell T, Smith CM: Headache and CNS white matter abnormalities associated with gluten sensitivity. Neurology 2001 Feb 13;56(3):385-8.

Abstract:

Department of Clinical Neurology, The Royal HallamshireHospital, Sheffield,UK. m.hadjivassiliou@sheffield.ac.uk

The authors describe 10 patients with gluten sensitivity and abnormal MRI. All experienced episodic headache, six had unsteadiness, and four had gait ataxia. MRI abnormalities varied from confluent areas of high signal throughout the white matter to foci of high signal scattered in both hemispheres. Symptomatic response to gluten-free diet was seen in nine patients.

Dubynin VA , Ivleva IuA, Malinovskaia IV, Kamenskii AA, Andreeva LA, Alfeeva LIu, Miasoedov NF: Changes in beta-casomorphine-7 effect on behavior of albino rat pups in postnatal development [Article in Russian]. Zh Vyssh Nerv Deiat Im I P Pavlova 2001 May-Jun;51(3):386-9.

Abstract:

Lomonosov State University, Institute of Molecular Genetics, Russian Academy of Sciences, Moscow.

The analgetic effect of heptapeptide beta-casomorphine-7 in newborn albino rats (20 mg/kg, i.p.) was recorded already 14 days after birth in the "hot plate" test. The first signs of a possible influence of the peptide on motor activity were observed only at the age of 28 days. They are expressed in impairment of motor coordination and change in locomotion level ("Opto-Varimex" test). The obtained evidence probably reflect the processes of discrete maturation of different components of the opioid system of the rat brain.

Furlano RI, Anthony A, Day R, Brown A, McGarvey L, Thomson MA, Davies SE, Berelowitz M, Forbes A, Wakefield AJ, Walker-Smith JA, Murch SH: Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. J Pediatr. 2001 Mar;138(3):366-72.

University Department of Paediatric Gastroenterology, the Inflammatory Bowel Diseases Study Group, Royal Free and University College School of Medicine, London, United Kingdom.

OBJECTIVES: We have reported colitis with ileal lymphoid nodular hyperplasia (LNH) in children with regressive autism. The aims of this study were to characterize this lesion and determine whether LNH is specific for autism. METHODS: Ileo-colonoscopy was performed in 21 consecutively evaluated children with autistic spectrum disorders and bowel symptoms. Blinded comparison was made with 8 children with histologically normal ileum and colon, 10 developmentally normal children with ileal LNH, 15 with Crohn's disease, and 14 with ulcerative colitis. Immunohistochemistry was performed for cell lineage and functional markers, and histochemistry was performed for glycosaminoglycans and basement membrane thickness. RESULTS: Histology demonstrated lymphocytic colitis in the autistic children, less severe than classical inflammatory bowel disease. However, basement membrane thickness and mucosal gamma delta cell density were significantly increased above those of all other groups including patients with inflammatory bowel disease. CD8(+) density and intraepithelial lymphocyte numbers were higher than those in the Crohn's disease, LNH, and normal control groups; and CD3 and plasma cell density and crypt proliferation were higher than those in normal and LNH control groups. Epithelial, but not lamina propria, glycosaminoglycans were disrupted. However, the epithelium was HLA-DR(-), suggesting a predominantly T(H)2 response. INTERPRETATION: Immunohistochemistry confirms a distinct lymphocytic colitis in autistic spectrum disorders in which the epithelium appears particularly affected. This is consistent with increasing evidence for gut epithelial dysfunction in autism.

Cavataio F, Carroccio A, Iacono G.: Milk-induced reflux in infants less than one year of age. J Pediatr Gastroenterol Nutr 2000;30 Suppl:S36-44

Abstract:

1st Divisione Pediatria, Gastroenterologia, Ospedale dei Bambini G. Di Cristina, Palermo, Italy.

Cow's milk allergy (CMA) and gastroesophageal reflux are considered to be among the most common disturbances in infants less than 1 year of age. In recent years, the relationship existing between these two entities has been investigated and some important conclusions have been reached: In just under half the cases of GER in infants less than 1 year of age there is an association with CMA; in a high proportion of cases, GER is not only CMA-associated but also CMA-induced; the frequency of this association should induce pediatricians to screen for possible concomitant CMA in all infants with GER less than 1 year old; with the exception of some patients with mild typical CMA manifestations (diarrhea, dermatitis, or rhinitis), the symptoms of GER associated with CMA are the same as those observed in primary GER; immunologic tests are useful in a suspected association between GER and CMA; and subjects with GER secondary to CMA show a typical pH-monitoring tracing pattern, characterized by a progressive, slow decrease in esophageal pH between feedings. This article reviews the main features of the two diseases, stressing the aspects in common between them and comments on all the listed points.

NOTE: Reflux appears to be common in infants later dx'd with autism.

Carroccio A, Montalto G, Custro N, Notarbartolo A, Cavataio F, D'Amico D, Alabrese D, Iacono G: Evidence of very delayed clinical reactions to cow's milk in cow's milk-intolerant patients. Allergy 2000 Jun;55(6):574-9.

Abstract:

Internal Medicine, University Hospital of Palermo, Italy.

BACKGROUND: In patients with cow's milk protein intolerance (CMPI), delayed clinical reactions to cow's milk (CM) ingestion may be misdiagnosed if the clinical symptoms are not "classical" and there is a long time lapse between ingestion of CM and the clinical reaction. The aim was to evaluate the clinical outcome of CMPI in a cohort of CM-intolerant children, with particular attention to the occurrence of clinical manifestations beyond 72 h after CM challenge. METHODS: Eighty-six consecutive patients (44 boys, 42 girls) with new CMPI diagnoses were enrolled; median age at diagnosis was 4 months. Patients were followed up for a mean period of 40 months. In all patients, CMPI diagnosis was made on the observation of symptoms, their disappearance after elimination diet, and their reappearance on double-blind CM challenge. At CMPI diagnosis, immunologic tests to demonstrate IgE-mediated hypersensitivity were performed. After 12 months of CM-free diet, CM tolerance was re-evaluated with a CM challenge continued at home for up to 30 days, according to a double-blind, placebo-controlled method. Patients who did not achieve CM tolerance continued a CM-free diet and subsequently underwent yearly CM challenge. RESULTS: The percentages of CMPI patients who became CM-tolerant after 1, 2, and 3 years of CM-free diet were 30%, 54.5%, and 70%, respectively. At the end of the follow-up period, 26/86 subjects showed persistent CMPI; these patients had a higher percentage of positivity of total serum IgE ($P<0.05$), RAST ($P<0.01$), and cutaneous prick tests for CM antigens ($P<0.001$) than all the others. At CMPI diagnosis, all patients had a clinical reaction within 72 h from the beginning of the CM challenge; at the subsequent "cure" challenges, we observed patients who first reacted to CM more than 72 h after ingestion. In total, 10 out of 86 patients showed "very delayed reactions"; in these patients, the mean time between the beginning of CM challenge and the onset of a clinical symptom was 13.3 days (range 4-26 days). The number of "very late reactors" increased from the first to the third of the "cure" CM challenges, performed at yearly intervals. The "very delayed" CMPI manifestations in these subjects were constipation (five cases), wheezing (two cases), dermatitis plus constipation (two cases), and dermatitis alone (one case); in 6/10 patients, the symptoms observed at the "cure challenge" were different from those at CMPI onset. CONCLUSIONS: Very delayed clinical reactions to reintroduction of CM in the diet can occur in CMPI patients; thus, accurate follow-up and frequent outpatient observation in patients with a long history of CMPI are probably more useful and safer than prolonged CM challenge.

Cade R, Privette M, Fregly M, Rowland N, Sun Z, Zele V, Wagemaker H, Edlestein C: Autism and schizophrenia: intestinal disorders. Nutritional Neuroscience 3: 57-72, 2000. [No abstract available]

Pedersen OS, Liu Y, Reichelt KL.: Serotonin uptake stimulating peptide found in plasma of normal individuals and in some autistic urines. J Pept Res 1999 Jun;53(6):641-6

Abstract:

Research Institute, University of Oslo, Rikshospitalet, Norway.

We have isolated a tripeptide from normal plasma and autistic urines which stimulates the uptake of serotonin (5-HT) into platelets. This peptide was purified by high-performance liquid chromatography (HPLC) and characterized by sequenation and mass-spectrometry. Synthetic peptide showed co-chromatography with the biological sample in the HPLC systems used. Close to 60% of the autistic children diagnosed using the Diagnostic Statistical Manual III-R had an increased HPLC peak eluting like this peptide in their urines compared with controls.

Ek J, Stensrud M, Reichelt KL.: Gluten-free diet decreases urinary peptide levels in children with celiac disease. J Pediatr Gastroenterol Nutr 1999 Sep;29(3):282-5.

Abstract:

Department of Pediatrics, Buskerud Central Hospital, Drammen, Norway.

BACKGROUND: Increased urine secretion of peptides has been found in celiac disease, probably resulting from increased intestinal uptake of peptides caused by damage to the small gut mucosa. METHODS: High-performance liquid chromatography of low-molecular-weight peptides in the urine was performed over 6 months, before and after a gluten-free diet was instituted in children who clinically improved while consuming the diet. RESULTS: A significant decrease of peptide levels was observed in children consuming the gluten-free diet. Certain peptide peaks thought to be gluten related decreased the most after the patients began the diet. CONCLUSIONS: Because the peptides decrease in patients consuming a gluten-free diet, it is reasonable to conclude that such peptides have a mostly dietary origin.

Cade JR et al: Autism and schizophrenia linked to malfunctioning enzyme for milk protein digestion. Autism, Mar 1999.

- Sun Z, Cade JR, Fregly MJ, Privette RM. Caesomorphine induces Fos-like reactivity in discrete brain regions relevant to schizophrenia and autism. Autism 1999;3:67-84
- Sun Z, Cade JR. A peptide found in schizophrenia and autism causes behavioral changes in rats. Autism 1999;3:85

Cade JR, Privette RM, Fregly M, Rowland N, Sun Z, Zele V, Wagemaker H Edelstein C: Autism and schizophrenia: Intestinal disorders. Nutritional Neuroscience 1999, 2, 57-72.

Alberti A, Pirrone P, Elia M, Waring RH, Romano C: Sulphation deficit in "low-functioning" autistic children: a pilot study. Biol Psychiatry 1999 Aug 1;46(3):420-4.

Abstract:

Department of Pediatrics, Oasi Institute for Research on Mental Retardation and Brain Aging (IRCCS), Troina, Italy.

BACKGROUND: Parents of autistic children and autism support groups often report that autistic episodes are exacerbated when the children eat certain foodstuffs such as dairy products, chocolates, wheat, corn sugar, apples, and bananas. The hypothesis that autistic behavior might be related to metabolic dysfunctions has led us to investigate in a group of "low functioning" autistic children and in an age-matched control group each made up of 20 subjects, the sulphation capacity available. METHODS: Utilizing the biochemical characteristics of paracetamol we evaluated by high performance liquid chromatography, the urine paracetamol-sulfate/paracetamol-glucuronide (PS/PG) ratio in all subjects following administration of this drug. RESULTS: The PS/PG ratio in the group of autistic subjects gave a significantly lower results than the control group with $p < .00002$. CONCLUSIONS: The inability to effectively metabolize certain compounds particularly phenolic amines, toxic for the CNS, could exacerbate the wide spectrum of autistic behavior.

Iacono G, Cavataio F, Montalto G, Florena A, Tumminello M, Soresi M, Notarbartolo A, Carroccio A: Intolerance of cow's milk and chronic constipation in children. New England Journal of Medicine 1998 / 339 (16) / 1100-1104.

Abstract:

Divisione di Pediatria, Ospedale G. Di Cristina, Palermo, Italy.

BACKGROUND: Chronic diarrhea is the most common gastrointestinal symptom of intolerance of cow's milk among children. On the basis of a prior open study, we hypothesized that intolerance of cow's milk can also cause severe perianal lesions with pain on defecation and consequent constipation in young children. METHODS: We performed a double-blind, crossover study comparing cow's milk with soy milk in 65 children (age range, 11 to 72 months) with chronic constipation (defined as having one bowel movement every 3 to 15 days). All had been referred to a pediatric gastroenterology clinic and had previously been treated with laxatives without success; 49 had anal fissures and perianal erythema or edema. After 15 days of observation, the patients received cow's milk or soy milk for two weeks. After a one-week washout period, the feedings were reversed. A response was defined as eight or more bowel movements during a treatment period. RESULTS: Forty-four of the 65 children (68 percent) had a response while receiving soy milk. Anal fissures and pain with defecation resolved. None of the children who received cow's milk had a response. In all 44 children with a response, the response was confirmed with a double-blind challenge with cow's milk. Children with a response had a higher frequency of coexistent rhinitis, dermatitis, or bronchospasm than those with no response (11 of 44 children vs. 1 of 21, $P=0.05$); they were also more likely to have anal fissures and erythema or edema at base line (40 of 44 vs. 9 of 21, $P<0.001$), evidence of inflammation of the rectal mucosa on biopsy (26 of 44 vs. 5 of 21, $P=0.008$), and signs of hypersensitivity, such as specific IgE antibodies to cow's-milk antigens (31 of 44 vs. 4 of 21, $P<0.001$). CONCLUSIONS: In young children, chronic constipation can be a manifestation of intolerance of cow's milk.

Iacono G, Cavataio F, Montalto G, Soresi M, Notarbartolo A, Carroccio A: Persistent cow's milk protein intolerance in infants: the changing faces of the same disease. Clin Exp Allergy 1998 Jul;28(7):817-23.

Abstract:

II Divisione di Pediatria, Ospedale Di Cristina, Universita di Palermo, Italy.

BACKGROUND: Recent research has shown that cow's milk protein intolerance (CMPI) often persists beyond 4 years of age. AIMS: To evaluate the clinical and immunological characteristics

of a group of infants with persistent CMPI. PATIENTS AND METHODS: Twelve infants (6 m, 6f) with persistent CMPI were followed up from birth until a median age of 5 years. The patients underwent CMP challenge each year to evaluate CMP-tolerance. As controls we followed 26 infants (12 m, 14 f) with CMPI that resolved within 1-2 years. RESULTS: A family history of atopic disease was found in 10/12 patients with persistent CMPI and in 10/26 controls (P<0.01). Clinical presentation changed over time: at onset symptoms were prevalently gastrointestinal, while at the end of the study there was an increased frequency of wheezing and constipation and a higher frequency of delayed reactions to CMP-challenge than at study commencement (9/12 vs 2/12; P<0.007). 11/12 infants with persistent CMPI and 3/26 controls (P<0.0001) presented multiple food intolerance. During the observation period 9/12 infants with persistent CMPI and 2/26 controls showed atopic disease: asthma, rhinitis, eczema (P < 0.0001). CONCLUSIONS: Persistent CMPI forms are characterized by: (a) considerable importance of familial atopic disease; (b) change in CMPI manifestations over time and more prolonged delay between CMP consumption and manifestation of symptoms; (c) very high frequency of multiple food intolerance and allergic diseases.

Teschemacher, H. et al: Milk protein-derived opioid receptor ligands. Biopolymers. 1997 / 43 (2) / 99-117.

Abstract:

Rudolf-Buchheim-Institut fur Pharmakologie, Justus-Liebig-Universitat, Giessen, Germany.

Milk is mammalian characteristic and is of particular importance for humans: Mother's milk or its substitutes from cows' milk are absolutely essential nutriments for the neonate and cows' milk also represents a basic foodstuff for adults. However, in addition to their well-known nutritive role, milk constituents apparently are also able to carry specific information from the milk producer's to the milk receiver's organism: Thus, a number of milk protein fragments has been shown to behave like opioid receptor ligands able to address opioidergic systems in the adult's or in the neonate's organism. With respect to the proteins, which they are derived off these peptides have been named alpha-casein exorphins or casoxin D (alpha-casein), beta-casomorphins or beta-casorphin (beta-casein), casoxin or casoxin A, B, or C (k-casein), alpha-lactorphins (alpha-lactalbumin), beta-lactorphin (beta-lactoglobulin) or lactoferroxins (lactoferrin). Only casoxins and lactoferroxins display antagonistic properties; the other peptides behave like opioid receptor agonists. Most of the information available so far has been collected about beta-casomorphins. These peptides obviously can be released from beta-casein in the adult's or in the neonate's organism, where they might elicit opioid effects in the frame of a regulatory role as "food hormones". Several synthetic beta-casomorphin derivatives have been shown to be highly specific and potent mu-type opioid receptor ligands which frequently have been used as standard tools in opioid research.

Fukudome, S. et al: Release of opioid peptides, gluten exorphins by the action of pancreatic elastase. FEBS Lett. 1997 / 412 (3) / 475-479.

Abstract:

Food Research Laboratory, Nisshin Flour Milling Co. Ltd., Saitama, Japan.

The release of opioid peptides, gluten exorphins A, which have been isolated from the pepsin-thermolysin digest of wheat gluten, with gastrointestinal proteases was examined. High levels of gluten exorphin A5 (Gly-Tyr-Tyr-Pro-Thr) immunoreactive materials were detected in the pepsin-pancreatic elastase digest by a competitive ELISA. From this digest, gluten exorphin A5, B5 and B4 were isolated. This means that these peptides are released in the gastrointestinal tracts after ingestion of wheat gluten. The yield of gluten exorphin A5 in the pepsin-elastase digest was larger than that in the pepsin-thermolysin digest. The gluten exorphin A5 sequence is found 15 times in the primary structure of the high molecular weight glutenin. The region from which gluten exorphin A5 was released by the action of pancreatic elastase was identified using synthetic fragment peptides.

Scifo R, Cioni M, Nicolosi A, Batticane N, Tirolo C, Testa N, Quattropani MC, Morale MC, Gallo F, Marchetti B: Opioid-immune interactions in autism: behavioural and immunological assessment during a double-blind treatment with naltrexone. Ann Ist Super Sanita 1996;32(3):351-9.

Abstract:

Servizio di Psichiatria, Istituto OASI per lo Studio del Ritardo Mentale e l'Involuzione Cerebrale, Troina (Enna), Italy.

The emerging concept of opioid peptides as a new class of chemical messengers of the neuroimmune axis and the presence of a number of immunological abnormalities in infantile autism prompted us to correlate biological (hormonal and immunological) determinations and behavioural performances during treatment with the potent opiate antagonist, naltrexone (NAL). Twelve autistic patients ranging from7 to 15 years, diagnosed according to DSM-III-R, entered a double-blind crossover study with NAL at the doses of 0.5, 1.0 and 1.5 mg/kg every 48 hours. The behavioural evaluation was conducted using the specific BSE and CARS rating scales NAL treatment produced a significant reduction of the autistic symptomatology in seven ("responders") out of 12 children. The behavioural improvement was accompanied by alterations in the distribution of the major lymphocyte subsets, with a significant increase of the T-helper-inducers (CD4+CD8-) and a significant reduction of the T-cytotoxic-suppressor (CD4-CD8+) resulting in a normalization of the CD4/CD8 ratio. Changes in natural killer cells and activity were inversely related to plasma beta-endorphin levels. It is suggested that the mechanisms underlying opioid-immune interactions are altered in this population of autistic children and that an immunological screening may have prognostic value for the pharmacological therapy with opiate antagonists.

Hadjivassiliou M, Gibson A, Davies-Jones GA , Lobo AJ, Stephenson TJ, Milford-Ward A: Does cryptic gluten sensitivity play a part in neurological illness? Lancet 1996 Feb 10;347(8998):369-71.

Abstract:

Department of Neurology, Royal Hallamshire Hospital, Sheffield, UK.

BACKGROUND: Antigliadin antibodies are a marker of untreated coeliac disease but can also be found in individuals with normal small-bowel mucosa. Because neurological dysfunction is a known complication of coeliac disease we have investigated the frequency of antigliadin antibodies, as a measure of cryptic gluten sensitivity, and coeliac disease in neurological patients. METHODS: Using ELISA, we estimated serum IgG and IgA antigliadin antibodies in 147 neurological patients who were divided into two groups. There were 53 patients with neurological dysfunction of unknown cause despite full investigation (25 ataxia, 20 peripheral neuropathy, 5 mononeuritis multiplex, 4 myopathy, 3 motor neuropathy, 2 myelopathy). The remaining 94 patients were found to have a specific neurological diagnosis (16 stroke, 12 multiple sclerosis, 10 Parkinson's disease, 56 other diagnoses) and formed the neurological control group. 50 healthy blood donors formed a third group. FINDINGS: The proportions of individuals with positive titres for antigliadin antibodies in the three groups were 30/53, 5/94, and 6/50 respectively (57, 5, and 12%). The difference in proportion between group 1 and the combined control groups was 0.49 (95% CI 0.35-0.63). Distal duodenal biopsies in 26 out of 30 antigliadin-positive patients from group 1 revealed histological evidence of coeliac disease in nine (35%), non-specific duodenitis in ten (38%), and no lesion in seven (26%) individuals. INTERPRETATION: Our data suggest that gluten sensitivity is common in patients with neurological disease of unknown cause and may have aetiological significance.

D'Eufemia P., Celli M., Finocchiaro R., Pacifico L., Viozzi L., Zaccagnini M., Cardi E., Giardini O: Abnormal Intestinal Permeability in Children with Autism. Acta Paediatrica,1996; 85: 1076-1079.

Abstract:

Institute ofPediatrics, La Sapienza University of Rome, Italy.

We determined the occurrence of gut mucosal damage using the intestinal permeability test in 21 autistic children who had no clinical and laboratory findings consistent with known intestinal disorders. An altered intestinal permeability was found in 9 of the 21 (43%) autistic patients, but in none of the 40 controls. Compared to the controls, these nine patients showed a similar mean mannitol recovery, but a significantly higher mean lactulose recovery (1.64% +/- 1.43 vs 0.38% +/- 0.14; P < 0.001). **We speculate that an altered intestinal permeability could represent a possible mechanism for the increased passage through the gut mucosa of peptides derived from foods with subsequent behavioural abnormalities.**

Lucarelli, S., Frediani, T., Zingoni, A.M., Ferruzzi, F.,Giardini, O., Quintieri, F., Barbato, M., D'Eufemia, P., Cardi, E.: Food allergy and infantile autism, Panminerva Med., 1995 Sep; 37(3): 137-41.

Abstract:

Department of Paediatrics, University of Rome La Sapienza, Italy.

The etiopathogenesis of infantile autism is still unknown. Recently some authors have suggested that food peptides might be able to determine toxic effects at the level of the central nervous system by interacting with neurotransmitters. In fact a worsening of neurological symptoms has been reported in autistic patients after the consumption of milk and wheat. The aim of the present study has been to verify the efficacy of a cow's milk free diet (or other foods which gave a positive result after a skin test) in 36 autistic patients. We also looked for immunological signs of food allergy in autistic patients on a free choice diet. We noticed a marked improvement in the behavioural symptoms of patients after a period of 8 weeks on an elimination diet and we found high levels of IgA antigen specific antibodies for casein, lactalbumin and beta-lactoglobulin and IgG and IgM for casein. The levels of these antibodies were significantly higher than those of a control group which consisted of 20 healthy children. Our results lead us to hypothesise a relationship between food allergy and infantile autism as has already been suggested for other disturbances of the central nervous system.

Lensing P, Schimke H, Klimesch W, Pap V, Szemes G, Klingler D, Panksepp J: Clinical case report: opiate antagonist and event-related desynchronization in 2 autistic boys. Neuropsychobiology 1995;31(1):16-23.

Abstract:

Department of Physiological Psychology, University of Salzburg, Austria.

Event-related desynchronization and visual orientational behavior were examined in 2 autistic boys to determine if blockade of endogenous opioid activity facilitates cognitive processing at a cortical level. Before naltrexone, the boys showed no selective alpha blocking during exposure to either mother's pictures or white light. Unlike normals, they exhibited strong alpha band enhancement at temporocentral recording sites. Two hours after administering 0.5 mg/kg naltrexone, mother-as well as light-related alpha blocking appeared at occipital, occipitotemporal, and

prefrontal sites. These effects were gone 24 h after dosing in one child, but persisted in the other. A parallel increase in visual pursuit in a social context was observed. These results affirm that autistic gaze aversion can be caused by excessive opioid activity interfering with corticothalamocortical processing of visual stimuli.

Kurek M, Czerwionka-Szaflarska M, Doroszewska G: Pseudoallergic
skin reactions to opiate sequences of bovine casein in healthy
children. Rocz Akad Med Bialymst 1995;40(3):480-5.

Abstract:

Department of Gastroenterology, Academy of Medicine, Gdansk.

Skin tests with opioid peptides naturally occurring in cow's milk: beta-casomorphin-7 and alpha-casein (90-95), were performed in 25 healthy children. Wheal and flare reactions, similiar to histamine and codeine were observed in all children. The area of these reactions was concentration dependent. Pretreatment with H1 antagonist--cetirizine significantly inhibited the skin response to both peptides. Beta-casomorphin-7 and alpha-casein (90-95) are noncytotoxic histamine releasers in humans.

Knivbserg A.M., Reichelt K.L., Nodland M., Hoien T.: Autistic syndromes and diet. A four year follow-up study. Scand J Educat. Res. 1995, 39: 223-236.

Abstract:

Dietary intervention was applied to 15 subjects with autistic syndromes, with pathological urine patterns, and increased levels of peptides found in their twenty-four-hour urine samples. The peptides, some of which are probably derived from gluten and casein, are thought to have a negative pharmacological effect on attention, brain maturation, social interaction and learning. Our hypothesis was that a diet without these proteins would facilitate learning. Social behaviour, as well as cognitive and communicative skills, were assessed before diet. The subjects were closely followed for a year, after which their urine was retested blind, and the assessment of behaviors and skills was repeated. Further retesting was made four years after the onset of dietary intervention. Normalization of urine patterns and peptide levels was found after one year. Likewise, a decrease in odd behaviour and an improvement in the use of social, cognitive and communicative skills were registered. This positive development continued through the next three years, though at a lower rate. These promising results encourage further research on the effect of dietary intervention.

Bouvard MP, Leboyer M, Launay JM, Recasens C, Plumet MH, Waller-Perotte D, Tabuteau F, Bondoux D, Dugas M, Lensing P, et al: Low-dose naltrexone effects on plasma chemistries and clinical symptoms in autism: a double-blind, placebo-controlled study. Psychiatry Res 1995 Oct 16;58(3):191-201.
Abstract:

Service de Psychopathologie de l'Enfant et de l'Adolescent, Hopital Robert Debre, Paris, France.

The effect of month-long naltrexone (NTX) treatment at a daily oral dose of 0.5 mg/kg/day was contrasted with placebo (PLC) in a double-blind study with conjoint clinical and biochemical evaluations of therapeutic effects. Modest clinical benefits were achieved with both PLC and NTX, with marginally better overall results following NTX, and degree of improvement appeared to be related to plasma chemical profiles. Massively elevated levels of beta-endorphin were observed in all children with assays using C-terminal antibody but not with an N-terminal antibody assay. In addition, 70% of the children exhibited abnormally low levels of adrenocorticotropic hormone, and smaller subsets exhibited elevated norepinephrine (60%), arginine-vasopressin (50%), and serotonin (20%). The best clinical responders exhibited the clearest normalization of the elevated plasma chemistries, especially in C-terminal-beta-endorphin and serotonin. There was some evidence of therapeutic carry-over effects in both clinical and biochemical measures in those children who received NTX before PLC. The results suggest that NTX only benefits a subgroup of autistic children, who may be identified by the presence of certain plasma abnormalities. These results suggest a possible linkage between abnormal plasma chemistries, especially those related to the pro-opiomelanocortin system, and autistic symptoms.

Reichelt K.L. Knivsberg AM, Nodland M, Lind G: Nature and consequences of hyperpeptiduria and bovine casomorphin found in autistic syndromes. Develop Brain Dysfunct. 1994, 7: 71-85. [No abstract available]

Gardner M.L.G.: Absorption of intact proteins and peptides. Physiol of gastrointestinal Tract 3rd edit (edit: LR Johnson) Raven press, New York 1994: 1795-1820.

Leboyer M, Bouvard MP, Launay JM, Recasens C, Plumet MH, Waller-Perotte D, Tabuteau F, Bondoux D, Dugas M: Opiate hypothesis in infantile autism? Therapeutic trials with naltrexone [Article in French]. Encephale 1993 Mar-Apr;19(2):95-102.

Abstract:

Service de Psychiatrie Adulte, Hopital Pitie-Salpetriere, Paris.

The opioid hypothesis suggests that childhood autism may result from excessive brain opioid activity during neonatal period which may constitutionally inhibit social motivation, yielding autistic isolation and aloofness (Panksepp, 1979). This hypothesis has now received strong support and is currently based on three types of arguments: (1) similarity between autistic symptomatology and abnormal behaviors induced in young animals by injections of exogenous opioids, such as increasing social aloofness and decreasing social vocalization; (2) direct biochemical evidence of abnormalities of peripheral endogenous opioids being reported in autism and (3) therapeutic effects of the long lasting opioid receptor blocking agent naltrexone in autism. In this article, we give description of open and double-blind studies of naltrexone in autism. Naltrexone has been tested in several open studies. We performed an open trial with naltrexone in 2 autistic girls, displaying serious self-injurious behavior, reduced crying and a marked preference for salty and spicy foods, symptoms that could be related to a dysfunction of the opioid system. With dosages of 1 mg/kg/day, we observed an immediate reduction of hyperactivity, self-injurious behavior and aggressiveness, while attention improved. In addition, social behaviors, smiling, social seeking behaviors and play interactions increased (Leboyer, Bouvard et Dugas, 1988). Campbell et al. (1988) has also reported a tranquilizing and a stimulating effect in 6 out of 8 children with autism. We did confirm these preliminary results in a double-blind study performed on 4 children with autism. In a cross-over double-blind study, three dosages of naltrexone (0.5, 1 and 2 mg/kg/day) and placebo were compared. (ABSTRACT TRUNCATED AT 250 WORDS)

Fukudome S, Yoshikawa M: Gluten exorphin C, A novel opioid peptide derived from wheat gluten. FEBS 1993; 316: 17-19.

Abstract:

Research Control Department, Nisshin Flour Milling Co., Ltd., Nihonbashi, Tokyo, Japan.

A novel opioid peptide, Tyr-Pro-Ile-Ser-Leu, was isolated from the pepsin-trypsin-chymotrypsin digest of wheat gluten. Its IC50 values were 40 microM and 13.5 microM in the GPI and MVD assays, respectively. This peptide was named gluten exorphin C. Gluten exorphin C had a structure quite different from any of the endogenous and exogenous opioid peptides ever reported in that the N terminal Tyr was the only aromatic amino acid. The analogs containing Tyr-Pro-X-Ser-Leu were synthesized to study its structure-, activi, , t, y relationship. Peptides in which X was an aromatic amino acid or an aliphatic hydrophobic amino acid had opioid activity.

Bidet B, Leboyer M, Descours B, Bouvard MP, Benveniste J: Allergic sensitization in infantile autism. J Autism Dev Disord 1993 Jun;23(2):419-20. [No abstract available.]

McLaughlin P.J., Zagon I.S.: Endogenous opiod systems and clinical implications for infantile autism. Proceedings of the International Symposium on Neurobiology of Infantile Autism, Tokyo , 1990, Neurobiology of Infantile Autism, Excerpta Medica 1992.

Lensing P, Klingler D, Lampl C, Leboyer M, Bouvard M, Plumet MH, Panksepp J: Naltrexone open trial with a 5-year-old-boy. A social rebound reaction. Acta Paedopsychiatr 1992;55(3):169-73.

Abstract:

School Psychology of Upper Austria, Linz.

The neurobiological rationale for an opiate antagonist pharmacotherapy of autism is presented. Naltrexone efficacy in decreasing autistic behaviour and in increasing social-affiliative behaviour was explored in a 5-year-old autistic boy. Naltrexone (0.5 mg/kg 3 times peer week) was effective in immediately decreasing gross motor activity and stereotyped behaviour and caused a delayed increase of crying, smiling and rough-and-tumble play. This single case presents preliminary evidence that a therapeutically valuable rebound reaction is possible and that the human opioid system modulates social-affective processes. The possibility of psychological factors being instrumental in achieving this effect is discussed as being suitable for future clinical trials.

Kurek M, Przybilla B, Hermann K, Ring J: A naturally occurring opioid peptide from cow's milk, beta-casomorphine-7, is a direct histamine releaser in man.Int Arch Allergy Immunol 1992;97(2):115-20.

Abstract:

Department of Dermatology, Ludwig-Maximilian-Univ, ersity, Munich.

beta-Casomorphine-7, a naturally, occurring product of cow's milk with opiate-like activity, was studied for possible direct histamine liberation activities in humans. It was found to cause concentration-dependent in vitro histamine release from peripheral leukocytes of healthy adult volunteers. Intradermal injection of beta-casomorphine-7 induced a wheal and flare reaction in the skin similar to histamine or codeine. Oral pretreatment with the H1 antagonist terfenadine significantly inhibited the skin responses to beta-casomorphine-7. The intradermal injection of an opiate receptor antagonist, naloxone, inhibited in vitro histamine release and skin reactions only in a 100-fold excess over beta-casomorphine-7. These findings suggest that beta-casomorphine-7 can be regarded as a noncytotoxic, direct histamine releaser in humans. The clinical relevance of these findings deserves further studies.

Fukudome S, Yoshikawa M: Opioid peptides derived from wheat gluten: their isolation and characterization. Federation of European Biochemical Societies (FEBS) 1992; 296: 107-111.

Abstract:

Research Control Department, Nisshin Flour Milling Co., Ltd., Tokyo, Japan.

Four opioid peptides were isolated from the enzymatic digest of wheat gluten. Their structures were Gly-Tyr-Tyr-Pro-Thr, Gly-Tyr-Tyr-Pro,Tyr-Gly-Gly-Trp-Leu and Tyr-Gly-Gly-Trp, which were named gluten exorphins A5, A4, B5 and B4, respectively. The gluten exorphin A5 sequence was found at 15 sites in the primary structure of the high molecular weight glutenin and was highly specific for delta-receptors. The structure-activity relationships of gluten exorphins A were unique in that the presence of Gly at their N-termini increased their activities. Gluten exorphin B5, which corresponds to [Trp4,Leu5]enkephalin, showed the most potent activity among these peptides. Its IC50 values were 0.05 microM and 0.017 microM, respectively, on the GPI and the MVD assays.

Dubynin VA, Maklakova AS, Nezavibat'ko VN, Alfeeva LA, Kamenskii AA, Ashmarin IP: Effects of systemically-administered beta-casomorphin-7 on nociception in rats. [Article in Russian] Biull Eksp Biol Med 1992 Sep;114(9):284-6.

Abstract:

The influence of food-derived heptapeptide beta-casomorphin-7 (beta-CM-7) on pain sensibility of white rats was studied by tail flick test. As shown for doses 10 and 20 mg/kg intraperitoneally, injected beta-CM-7 induced significant analgesia; lower peptide concentration (5 mg/kg) was ineffective. As a whole, there is a significant positive correlation between the intensity of analgesia and the quantity of administered exorphine. These changes of pain sensibility were observed for one hour after injection of heptapeptide; further measurements showed no significant difference of time reaction between control and experimental groups of rats. It was found out that animals with high native level of pain sensibility (4-8 sec) made the main contribution to manifestation of analgesia.

Bouvard M.P., Leboyer M., Launay J.M., Kerdelhue B., Dugas M.: The opiod excess hypothesis of autism: A double-blind study of naltrexone. Proc. of the Intern. Symp. on Neurob. of Inf. Autism, 1990, Neurobiology of Infantile Autism, Exerpta Medica 1992.

Teschemacher H, Koch G: Opioids in the milk. Endocr Regul 1991 Sep;25(3):147-50.

Abstract:

Rudolf-Buchheim-Institut fur Pharmakologie, Justus-Liebig-Universitat Giessen, Germany.

In various studies, the milk has been screened for the presence of free or precursor-bound opioids. In fact, various opioid receptor ligands with agonistic or even antagonistic activity were found. Besides the alkaloid morphine, peptides derived from alpha-casein (alpha-casein exorphins), beta-casein (beta-casomorphins; beta-casorphin), alpha-lactalbumin (alpha-lactorphins) and beta-lactoglobulin (beta-lactorphin) were among the agonists. In addition, certain peptides derived from k-casein (casoxins) or from lactoferrin (lactoferroxins) were found to behave like opioid antagonists. Although a functional role in the mammalian organism for all of these compounds appears to be well possible, evidence has only been presented for the functional significance of beta-casomorphins, so far. These peptides might play a role in reproduction or nutrition in the female, in the newborn's or in a milk consumer's organism, respectively. Thus, opioids related to milk might represent essential exogenous extensions of the endogenous opiodergic systems.

Risebro, B.: Gluten-free diet in infantile autism. Tidsskr Nor Laegeforen 1991 Jun 10;111(15):1885-6 [Article in Norwegian]

Reichelt K.L., Knivsberg A.M., Lind G., Nodland M.: The probable etiology and possible treatment of childhood autism. Brain Dysfunct. 1991, 4: 308-319. [No abstract available]

Longoni R, Spina L, Mulas A, Carboni E, Garau L, Melchiorri P, Di Chiara G: (D-Ala2)deltorphin II: D1-dependent stereotypies and stimulation of dopamine release in the nucleus accumbens. J Neurosci 1991 Jun;11(6):1565-76.

Abstract:

Institute of Experimental Pharmacology and Toxicology, University of Cagliari, Italy.

In order to investigate the relative role of central delta- and mu-opioid receptors in behavior, the effects of (D-Ala2)deltorphin II, a natural delta-opioid peptide, and PL017, a beta-casomorphin derivative specific for mu receptors, were compared after local intracerebral and intraventricular administration. Intracerebral infusion of the two peptides was done bilaterally in the limbic nucleus accumbens and in the ventral and dorsal caudate putamen of freely moving rats through chronic intracerebral cannulas. After intra-accumbens infusion, the two peptides elicited marked but opposite behavioral effects: while (D-Ala2)deltorphin II evoked dose-dependent motor stimulation characterized by locomotion, sniffing, and oral stereotypies, PL017 elicited motor inhibition with rigidity and catalepsy. These effects were site specific because they could not be evoked from the ventral or from the dorsal caudate. Low doses of naloxone (0.1 mg/kg, s.c.) blocked the effects of PL017 but not those of (D-Ala2)deltorphin II, which instead were reduced by high doses of naloxone (1.0 mg/kg) and by the putative delta-antagonist naltrindole; this drug failed to affect the catalepsy induced by PL017. Therefore, while (D-Ala2)deltorphin II effects were delta-mediated, PL017 effects were mu-mediated. Blockade of dopamine D1 receptors by SCH 23390 abolished (D-Ala2)deltorphin II effects, while blockade of dopamine D2 receptors by raclopride or by haloperidol was without effect. Local application by reverse dialysis of (D-Ala2)deltorphin II (5 microM) to the accumbens resulted in a naloxone-sensitive increase of extracellular dopamine concentrations; these effects could not be evoked from the caudate, nor by PL017 in the accumbens. Intracerebroventricular administration of (D-Ala2)deltorphin II or of PL017 elicited behavioral effects qualitatively similar to those obtained from the accumbens.

If deltorphin II is indeed present in the urine, this may explain why low doses of naloxone are often only moderately effective at reducing autistic behaviors.

Fukudome S.-I. and Yoshikawa M.: Opioid peptides derived from wheat gluten: Their isolation and characterization. FEBS Letters 1991, 296: 107-111.

Abstract:

Four opioid peptides were isolated from the enzymatic digest of wheat gluten. Their structures were Gly-Tyr-Tyr-Pro-Thr, Gly-Tyr-Tyr-Pro, Tyr-Gly-Gly-Trp-Leu and Tyr-Gly-Gly-Trp, which were named gluten exorphins A5, A4, B5 and B4, respectively. The gluten exorphin A5 sequence was found at 15 sites in the primary structure of the high molecular weight glutenin and was highly specific for delta-receptors. The structure-activity relationships of gluten exorphins A were unique in that the presence of Gly at their N-termini increased their activities. Gluten exorphin B5, which corresponds to [Trp4,Leu5]enkephalin, showed the most potent activity among these peptides. Its IC50 values were 0.05 microM and 0.017 microM, respectively, on the GPI and the MVD assays.

Shattock P. Kennedy A, Rowell F, Berney T: Role of neuropeptides in autism and their relationships with classical neurotransmitters. Brain Dysfunct 1990, 3: 328-346. [No abstract available]

Reichelt K.L., Ekrem J., Scott H.: Gluten, milk proteins and autism: Dietary interventions effects on behavior and peptide secretion. J Appl Nutrition 1990, 42: 1-11. [No abstract available]

Marchetti B, Scifo R, Batticane N, Scapagnini U: Immunological Significance of Opioid Peptide Dysfunction in Infantile Autism. Brain Dysfunction,3: 346-354,1990. [No abstract available]

Leboyer M, Bouvard MP, Lensing P, Launay JM, Tabuteau F, Arnaud P, Waller D, Plumet MH, Recasens C, Kerdelhue B, Dugas M, Panksepp J: Opioid Excess Hypothesis of Autism. Brain Dysfunction 1990; 3: 285-298. [No abstract available]

Knivsberg A.M., Wiig K., Lind G., Nodland M., Reichelt K.L.: Dietary intervention in autistic syndromes. Brain Dysfunc. 1990, 3: 315-327. [No abstract available]

Cade R. et al.: The effects of dialysis and diet in schizophrenia. Psychiatry: A World perspective 1990, 3: 494-500. [No abstract available]

Barthelemy C, Bruneau N, Adrien J, Roux S, Lelord G: Clinical, Biological and Therapeutic Applications of the Functional Analysis of Autistic Disorders. Brain Dysfunction, 3: 271-284, 1990. [No abstract available]

Herrera-Marschitz M, Terenius L, Grehn L, Ungerstedt U: Rotational behaviour produced by intranigral injections of bovine and human beta-casomorphins in rats. Psychopharmacology (Berl) 1989;99(3):357-61.

Abstract:

Department of Pharmacology, Karolinska Institutet, Stockholm, Sweden.

The biological activity of beta-casein derived beta-casomorphin peptides was evaluated by injecting bovine beta-casomorphin-5 (Tyr-Pro-Phe-Pro-Gly), the homologous sequence in human beta-casein (Tyr-Pro-Phe-Val-Glu) and the corresponding N-terminal tetrapeptides into the left substantia nigra of rats. Their ability to produce rotational behaviour was compared to that produced by three reference compounds, morphine, D-ala2D-leu5 enkephalin and U50,488H, ligands for mu, delta and kappa types of opioid receptors, respectively. The relative potencies of beta-casomorphins and morphine were compared to those tested in two in vitro assays for opioid activity: (1) inhibition of the electrically induced contraction of the isolated myenteric plexus-longitudinal muscle of the guinea-pig ileum and (2) displacement of 3H-dihydromorphine binding to brain membranes. The same ranking order of potency was found in all three assays, the peptides from human beta-casein being about 10-fold less potent than those from bovine beta-casein. The effects of both morphine and bovine beta-casomorphin-5 in producing rotational behaviour were antagonized by naloxone; however, approximately 10-fold more naloxone was required to antagonize the beta-casomorphin-5 effect than that of morphine. The present data are discussed in the light of the recent observation that high concentrations of beta-casomorphin-like peptides are found in the cerebrospinal fluid and plasma of women with postpartum psychosis.

Ramabadran K, Bansinath M: Opioid peptides from milk as a possible cause of sudden infant death syndrome. Med Hypotheses 1988 Nov;27(3):181-7.

Abstract:

Department of Anesthesiology, New York University Medical Center, NY 10016.

Milk from breast or baby formula is the exclusive source of nutrition for newborn infants. Short chain opioid peptides such as beta-casomorphins have been isolated from breast milk as well as

baby formula. These biologically active peptides are absorbed from the gastrointestinal tract. In infants predisposed to respiratory apnea because of abnormal autonomic nervous system development and respiratory control mechanisms, opioid peptides derived from milk might be one of the etiological factors for sudden infant death syndrome and near miss sudden infant death syndrome.

Paroli E: Opioid Peptides from Food (the Exorphins). World Review of Nutrition and Dietetics 1988; 55: 58-97. [No abstract available]

Hole K. et al.: Attention deficit disorders: A study of peptide-containing urinary complexes. J Develop Behav Pediatrics 1988, 9: 205-212.

Abstract:

Department of Physiology, University of Bergen, Norway.

In several behavioral disorders, we have observed that abnormal amounts of peptides and protein-associated peptide complexes are excreted in the urine. The gel filtration patterns of these excreted substances have some specificity for the different disorders. The urinary excretion of peptide-containing complexes was studied in 91 boys and 13 girls (mean age 9.4 years, range 1-23) with the clinical diagnosis of attention deficit disorder (ADD), with or without hyperactivity. The gel filtration of urine precipitate showed patterns in all patients that were different from those seen in 36 normal controls. Sixty-four patients had increased benzoic acid-glycoprotein-peptide complexes in the late peaks. The symptoms of all these patients fit the criteria for diagnosis of attention deficit disorder with hyperactivity (ADDH). Thirty-five patients showed reduced amounts of uric acid complexes in the late peaks. Clinically, this group, with the exception of three patients, fit the criteria for diagnosis of attention deficit disorder without hyperactivity. Five patients showed reduced amounts of all urinary complexes; four of these were hyperactive. Moderate exercise in control children did not change the urinary pattern. One urinary peptide fraction from hyperactive patients, purified to homogeneity, increased the uptake of 14C[5-HT] in platelets. Strict clinical, neuropsychological, and psychophysiological selection of the patients reduced the heterogeneity of the patterns. Although more studies are needed, the findings seem promising for the possibility of developing biochemical tests that may be helpful diagnostically.

Dohan, FC: Genetic hypothesis of idiopathic schizophrenia: its exorphin connection. Schizophr. Bull. 1988 / 14 (4) / 489-494.

Abstract:

Medical College of Pennsylvania, Eastern Pennsylvania, Psychiatric Institute, Philadelphia, 19129.

This brief overview proposes a testable oligogenic model of the inheritance of susceptibility to idiopathic schizophrenia: "abnormal" genes at each of a few complementary loci. The model is based on my assumptions as to the likely genetic abnormalities at possibly four or five interacting loci that would permit exorphins, the opioid peptides from some food proteins, especially glutens and possibly caseins, to go from gut to brain and cause symptoms of schizophrenia. Exorphins may reach the brain cerebrospinal fluid (CSF) in harmful amounts because of their genetically increased, receptor-mediated transcellular passage across the gut epithelial barrier plus decreased catabolism by genetically defective enzymes. A schizophrenia-specific, genetically enhanced affinity for exorphins by opioid receptors influencing dopaminergic and other neurons would permit sustained dysfunction at low CSF exorphin concentrations. Tests of each postulated genetic abnormality are suggested. This model is supported by a variety of evidence, including a significant effect of gluten or its absence on relapsed schizophrenic patients, the high correlation of changes in first admission rates for schizophrenia with changes in grain consumption rates, and the rarity of cases of schizophrenia where grains and milk are rare.

Sahley TL, Panksepp J: Brain opioids and autism: an updated analysis of possible linkages. J Autism Dev Disord 1987 Jun;17(2):201-16.

Abstract:

Considerable clinical evidence suggests that autistic children lack the normal ability or desire to engage others socially, as indicated by their poor social skills and inappropriate use of language for communicative purposes. Specifically, these children seem to lack normal amounts of social-emotional interest in other people, leading perhaps to a decreased initiative to communicate. This paper summarizes experimental evidence supporting a neurological theory, which posits that autism, at least partially, represents in the brain, such as brain opioids. These substances modulate social-emotional processes, and the possibility that blockade of opioid activity in the brain may be therapeutic for early childhood autism is discussed.

Kahn A, Rebuffat E, Blum D, Casimir G, Duchateau J, Mozin MJ, Jost R: Difficulty in initiating and maintaining sleep associated with cow's milk allergy in infants. Sleep 1987 Apr;10(2):116-21.

Abstract:

To confirm that sleeplessness in infants can be related to an undiagnosed allergy to cow's milk proteins, 71 infants were studied. Group I consisted of 20 infants referred for chronic insomnia that had appeared in the early days of life. Group II was made up of 31 infants admitted for skin or digestive symptoms attributed to cow's milk intolerance; 13 of these infants were shown to sleep as poorly as the infants of group I. Group III consisted of 20 infants with no history of sleep disturbance or milk allergy. The three groups of infants were comparable for sex and age. Laboratory tests revealed immunologic reactions to milk in all the infants in groups I and II. The sleep of the insomniac infants (group I, and the 13 "poor sleepers" in group II) became normal after cow's milk was eliminated from the diet. Insomnia reappeared when the infants in group I were challenged with milk. We conclude that infants with clinically evident milk allergy may suffer from sleeplessness and that when no evident cause for a chronic insomnia can be found in an infant the possibility of milk allergy should be given serious consideration.

Meisel, H: Chemical characterization and opioid activity of an exorphin isolated from in vivo digests of casein. FEBS Lett. 1986 / 196 (2) / 223-227.

Abstract:

The in vivo formation of an opioid peptide (exorphin) derived from beta-casein has been proved for the first time. It was isolated from duodenal chyme of minipigs after feeding with the milk protein casein. The exorphin has been identified as a beta-casein fragment by end-group determinations and qualitative amino acid analysis of the purified peptide. This peptide, named beta-casomorphin-11, displayed substantial opioid activity in an opiate receptor-binding assay.

Alpers DH: Uptake and fate of absorbed amino acids and peptides in the mammalian intestine. Federation Proc. 1986; 45:2261-2267.

Abstract:

Intraluminal and brush-border digestion of proteins results in a mixture of amino acids and small peptides. Thirteen brush-border peptidases have been described. Despite all of these enzymes, some peptides escape digestion and are absorbed intact. The assimilated products of protein digestion can follow multiple paths: absorption into the blood as amino acids or small peptides, metabolism within the enterocyte, incorporation into proteins of the enterocyte, and incorporation into proteins to be secreted into plasma. Unlike other tissues, the intestinal mucosa is not very responsive to metabolic regulation as regards amino acid uptake or regulation of protein synthesis. Most effects after dietary manipulation or drug or hormonal stimulation are modes (two-to fivefold increases). This constitutive metabolism of amino acids in the intestinal mucosa is consistent with its essential role in absorption. The mucosa also is a major contributor to apolipoproteins, which are probably the quantitatively most important proteins secreted from the intestine. Alterations in apoprotein secretion have been noted after fat feeding, and are both transcriptionally and translationally regulated. Although the fractional renewal rate of protein in the intestine is the highest of any tissue in the body, the quantitative importance of alterations in protein synthesis or secretion to the fate of intracellular amino acids is not known.

Svedberg, J.et al: Demonstration of beta-casomorphin immunoreactive materials in in vitro digests of bovine milk and in small intestine contents after bovine milk ingestion in adult humans. Peptides 1985 / 6 / pag.825-830.

Abstract:

Healthy young volunteers ingested one liter of cows' milk; then the contents of the small intestine were aspirated through an intestinal tube at various times and assayed for the presence of bovine beta-casomorphin immunoreactive materials. Considerable amounts of beta-casomorphin-7, but no beta-casomorphin-5 and only small amounts of beta-casomorphin-4 or -6 immunoreactive materials were found. Chromatographical characterization showed that most of the beta-casomorphin-7 immunoreactive material was not identical with beta-casomorphin-7, whereas the major part of the beta-casomorphin-4 or -6 immunoreactive materials might be identical with their corresponding beta-casomorphins. Analogous results were obtained for in vitro digestion of bovine milk which had been designed as a rough imitation of the gastrointestinal digestion process. A regulatory influence of beta-casomorphins as "food hormones" on intestinal functions is suggested.

Saelid G, et. al.: Peptide-Containing Fractions in Depression. Biol Psychiatry 1985, 20: 245-256.

Abstract:

A mixture of peptides and glycoproteins has been found in benzoic acid-precipitable material from urines of psychomotorically agitated and retarded endogenous depressive patients. This complex mixture of compounds is fractionated on a Sephadex G-25 gel, from which the different peaks are further separated on Biogel P2. The G-25 elution profiles ultraviolet absorbance, 280 nm) from depressive patients deviated from the normal pattern. The increase in hydrolyzable ninhydrin-colorable material of the P2 fractionation step encountered in psychotic depression was several-fold that of the normal population. Neurochemically active peptide-containing fractions were found. As explanation of these findings, it is probable that a genetically determined peptidase insufficiency is present, causing a peptide overflow when the secretion outstrips the breakdown. This model could easily combine more psychodynamic models with the genetic-biological models. The variability of the peptide patterns could possibly reflect the considerable clinical variability of the syndrome. Furthermore, the presence of a group of active compounds with different neuropharmacological activities might reflect the composite nature of the depressive syndrome.

Rix KJ, Ditchfield J, Freed DL, Goldberg DP, Hillier VF: Food antibodies in acute psychoses. Psychol Med 1985 May;15(2):347-54.

Abstract:

Antibodies to a variety of foods, and in particular cereals, were measured in serum from 100 patients with acute psychoses and 100 elective surgical patients. For 13 out of 14 foods to which non-IgE antibodies were detected the schizophrenics had slightly more antibodies than the controls. There was an association between a possible secondary mania and the presence of IgE antibodies to wheat or rye. However, neither the schizophrenia nor the mania findings can be regarded as evidence for food allergy causing psychiatric disorder, since the immunological findings in both cases may represent consequences of the illnesses or their treatment, rather than causes of the illness.

Chang, KJ, Su YF, Brent DA, Chang JK: Isolation of a specific mu-opiate receptor peptide, morphiceptin, from an enzymatic digest of milk proteins. J. Biol. Chem. 1985 / 260 (17) / pag. 9706-9712.

Abstract:

Specific radioimmunoassays have been developed for the measurement of naturally occurring morphiceptin and beta-casomorphin. These peptides and related exorphins were isolated from an enzymatic digest of caseins by chromatographic techniques including gel filtration, hydrophobic column and multiple-step high pressure liquid chromatography. Three exorphins were purified and characterized in their radioimmunological, biological, and chemical properties. They were identified as morphiceptin, beta-casomorphin, and 8-prolyl-beta-casomorphin. Since morphiceptin is a highly specific mu-agonist and can be derived from a milk protein, it is possible that morphiceptin is an exogenous opioid ligand specific for mu-receptors in the brain and gastrointestinal tract.

Takahashi M, Fukunaga H, Kaneto H, Fukudome S, Yoshikawa M: Behavioral and pharmacological studies on gluten exorphin A5, a newly isolated bioactive food protein fragment, in mice. Jpn J Pharmacol 2000 Nov;1984(3):259-65.

Abstract:

Department of Pharmacoinformatics, School of Pharmaceutical Sciences, Nagasaki University, Japan. takahashi@net.nagasaki-u.ac.jp

Central effects of gluten exorphin A5 (Gly-Tyr-Tyr-Pro-Thr), a fragment from wheat gluten, were studied on the pain-inhibitory system, emotionality and learning/memory processes in mice. Orally administered gluten exorphin A5 produced neither an antinociceptive effect nor an effect on morphine analgesia. Intracerebroventricularly (i.c.v.) administered gluten exorphin A5 produced mild but significant antinociception in a dose-depepndent manner, while not affecting the morphine analgesia. On the other hand, oral gluten exorphin A5 suppressed the endogenous pain-inhibitory system, i.e., antinociception induced by socio-psychological- (PSY-) stress (SIA) using a communication box; intraperitoneal gluten exorphin A5 abolished both footshock- (FS-) stress-induced antinociception (SIA) and PSY-SIA; and i.c.v. gluten exorphin A5 suppressed FS-SIA, but rather potentiated PSY-SIA. This peptide given by these routes was without effect on forced swim-SIA. In addition, oral gluten exorphin A5 tended to prolong the retention time on open arms in the elevated plus-maze test. Finally, oral gluten exorphin A5 when given during the post-training period of learning/memory processes significantly increased the latency into the dark compartment in the one-trail step-though type passive avoidance test, indicating that the peptide also facilitates the acquire/consolidation process of learning/memory. Thus, gluten exorphin A5 has been found to produce various effects not only in the peripheral nervous systems but also in the central nervous system.

Pfeiffer CC: Schizophrenia and wheat gluten enteropathy. Biol Psychiatry 1984 Mar;19(3):279-80. [No abstract available]

Lindstrom LH, Nyberg F, Terenius L, Bauer K, Besev G, Gunne LM, Lyrenas S, Willdeck-Lund G, Lindberg B: (1984) CSF and plasma beta-casomorphin-like opioid peptides in post-partum psychosis. Amer. J. Psychiat. 1984, 141: 1059-1066.

Abstract:

The authors measured opioid receptor-active components in the CSF of 11 women with postpartum psychosis, 11 healthy lactating women, and 16 healthy women who were not lactating. Activity that eluted with 0.2 M acetic acid 0.7-0.9 times the total volume of the column (fraction II activity) was significantly higher in the CSF of both healthy and psychotic women in the puerperium than in that of the lactating women. Very high levels of fraction II activity were seen in four psychotic patients. Material from these patients was further characterized by electrophoresis and high-performance liquid chromatography: The material migrated as bovine beta-casomorphin. Receptor-active material with the same characteristics was also found in the plasma of these four patients. The authors conclude that certain cases of postpartum psychosis are associated with the occurrence in plasma and CSF of unique opioid peptides probably related to bovine beta-casomorphin.

Huebner FR, Lieberman KW, Rubino RP, Wall JS: Demonstration of high opioid-like activity in isolated peptides from wheat gluten hydrolysates. Peptides 1984 Nov-Dec;5(6):1139-47.

Abstract:

Because of a possible relationship between schizophrenia and celiac disease, a condition in some individuals who are sensitive to wheat gluten proteins in the diet, there has been interest in observations that peptides derived from wheat gluten proteins exhibit opioid-like activity in in vitro tests. To determine the origin of the peptides exhibiting opioid activity, wheat proteins were fractionated by size (gel filtration), by charge differences (ion exchange chromatography) and by differences in hydrophobicity (reversed-phase HPLC). These fractions were hydrolyzed by pepsin or pepsin and trypsin and the resulting peptides separated by gel filtration chromatography. The separated peptides were tested for opioid-like activity by competitive binding to opioid receptor sites in rat brain tissue in the presence of tritium-labeled dihydromorphine. The peptides showed considerable differences in activity; while some peptides exhibited no activity, 0.5 mg of the most active peptides were equivalent to 1 nM of morphine in the binding assay. The most active peptides were derived from the gliadin fraction of the gluten complex.

Dohan et. al: "Is Schizophrenia Rare if Grain is Rare?" Biol Psychiat 1984; 19(3): 385-399.

Abstract:

If, as hypothesized, neuroactive peptides from grain glutens are the major agents evoking schizophrenia in those with the genotype(s), it should be rare if grain is rare. To test this, we analyzed the results of our clinical examinations (e.g., kuru) and observations of anthropologists on peoples consuming little or no grain. Only two overtly insane chronic schizophrenics were found among over 65,000 examined or closely observed adults in remote regions of Papua New Guinea (PNG, 1950-1967) and Malaita, Solomon Islands (1980-1981), and on Yap, Micronesia (1947-1948). In preneuroleptic Europe over 130 would have been expected. When these peoples became partially westernized and consumed wheat, barley beer, and rice, the prevalence reached European levels. Our findings agree with previous epidemiologic and experimental results indicating that grain glutens are harmful to schizophrenics.

Loukas, S. et al: Opioid activities and structures of alpha-casein-derived exorphins. Biochemistry 1983 / 22 (19) / 4567-4573.

Gardner MLG: Evidence for, and implications of, passage of intact peptides across the intestinal mucosa. Biochemical Society Transactions 1983; 11: 810-812. [no abstract available]

Morley, JE: Food peptides. A new class of hormones ? J. Am. Med. Assoc. 1982 / 247 (17) / 2379-2380. [No abstract available]

Reichelt KL, Hole K, Hamberger A, Saelid G, Edminson PD, Braestrup CB, Lingjaerde O, Ledaal P, Orbeck H: Biologically active peptide-containing fractions in schizophrenia and childhood autism. Adv Biochem Psychopharmacol 1981; 28: 627-643.

Abstract:

It is well documented that peptides have a major role in the effective functioning of higher animals at all levels from enzyme stabilization to homeostatic mechanisms governing essential functions such as eating, sexual behavior, and temperature regulation. The effects of exogenously administered peptides on neurotransmitter release, uptake, metabolism and behavioral consequences are also well established. We have attempted to extend these findings by postulating peptidergic neurons as transducers of multisignal inputs, and that development of pathological states may be due to genetically-determined reduced levels of activity of key peptidases, leading to excretion of regulatory peptides into the circulation. We have been able to demonstrate that, in schizophrenia and autism (in well defined clinical cases), the patterns of peptides and associated proteins from urinary samples differ considerably from each other and from normal controls. In addition to this, further purification of the material obtained has led to the discovery of a number of factors capable of modulating the function of major neurotransmitters. Some of these are in the final stages of characterization as peptides, while the remainder are also probably peptides, as purification has been followed by both biological testing and chemical analysis for peptidic material. We have outlined a number of parameters which we consider relevant in any attempt to put psychiatric disorders on a biological foundation. Any new advances in the neurochemical understanding of such disorders must take into consideration the observations of several different disciplines including genetics and psychology. However, at this stage of research it is far too early to speculate on the relevance of the various biological activities to the etiology and symptomatology of schizophrenia and childhood autism.

Trygstad OE, et al: Patterns of peptides and protein-associated-peptide complexes in psychiatric disorders. Br J Psychiatry 1980 Jan;136:59-72.

Abstract:

Peptidic neurones may be considered as multisignal intergrators and transducers. When formation or release of peptide outstrips genetically determined breakdown capacity, overflow of peptides to the body fluids and urine may be expected. In this paper, pathological urinary chromatographic patterns of peptides are shown for genetic, functional and mixed disorders. Part symptoms of the disorders may be induced with the biologically isolated and purified peptides as well as with chemically synthesized peptides.

Ross-Smith, P, Jenner FA: Diet (gluten) and Schizophrenia. J. Hum. Nutr. 1980 / 34 (2) / 107-112.

Four aspects of clinical evidence for an association between gluten and schizophrenia are examined. The scientific evidence for the role of gluten is set out. Finally, reference is made to other dietary approaches.

Zioudrou C, Streaty RA, Klee WA: Opioid peptides derived from food proteins. The exorphins. J. Biol. Chem.1979 / 254 (7) / 2446-2449.

Abstract:

Peptides with opioid activity are found in pepsin hydrolysates of wheat gluten and alpha-casein. The opioid activity of these peptides was demonstrated by use of the following bioassays: 1) naloxone-reversible inhibition of adenylate cyclase in homogenates of neuroblastoma X-glioma hybrid cells; 2) naloxone-reversible inhibition of electrically stimulated contractions of the mouse vas deferens; 3) displacement of [3H]dihydromorphine and [3H-Tyr, dAla2]met-enkephalin amide from rat brain membranes. Substances which stimulate adenylate cyclase and increase the contractions of the mouse vas deferens but do not bind to opiate receptors are also isolated from gluten hydrolysates. It is suggested that peptides derived from some food proteins may be of physiological importance.

Panksepp J: A neurochemical theory of autism. Point of View, North-Holland Biomedical Press, Jul 1979.

Hole K, Bergslien AA, Jørgensen H, Berge O-G, Reichelt KL & Trygstad OE:(1979) A peptide containing fraction from schizophrenia which stimulates opiate receptors and inhibits dopamine uptake. Neuroscience, 4, 1139-1147. [No abstract available]

Dohan FC: Schizophrenia and neuroactive peptides from food. Lancet 1979 May 12;1(8124):1031. [No abstract available]

Brantl V, Teschemacher H: Naunyn Schmiedebergs Arch Pharmacol 1979 Apr 30;306(3):301-4. A material with opioid activity in bovine milk and milk products.

Abstract:

Chloroform-methanol extracts of lyophilized milk, of commercially available dried milk or baby food and of casein digests were tested for opioid activity on the guinea-pig ileum longitudinal muscle-myenteric plexus preparation. Compounds with opioid activity--which proved to be resistant to peptidases--were detected in certain batches of baby food, casein digest, and cow milk in considerably varying amounts.

Ashkenazi et. al: "Immunologic reaction of psychotic patients to fractions of gluten" Am J Psychiat 1979; 136: 1306-1309.

Abstract:

Production of a leukocyte migration inhibition factor by peripheral blood lymphocytes in response to challenge with gluten fractions was studied in hospitalized patients with schizophrenia and other psychoses compared with normal individuals and with children and adolescents with celiac disease. The schizophrenic and other psychotic patients could be subdivided into two groups, one that responded in the leukocyte migration inhibition factor test as the celiac patients did and one that responded as the normal control subjects did. The psychotic and schizophrenic patients did not show any evidence of malabsorption. The authors speculate that gluten may be involved in biological processes in the brain in certain psychotic individuals.

O'Banion D, Armstrong B, Cummings RA, Stange J.: Disruptive behavior: a dietary approach. J Autism Child Schizophr 1978 Sep;8(3):325-37.

Abstract: The effect of particular foods on levels of hyperactivity, uncontrolled laughter, and disruptive behaviors was studied in an 8-year-old autistic boy. The floor of the child's room was taped off into six equal-sized rectangles to measure general activity level. Frequency data were recorded on screaming, biting, scratching, and object throwing. A time-sample technique was used to record data on laughing. Data were gathered during four phases. During an initial 4-day period the child was fed a normal American diet. A 6-day fasting period followed, during which time only spring water was allowed. The third phase lasted 18 days and involved the presentation of individual foods. During the final phase of the study the child was given only foods that had not provoked a reaction in the third phase. Results showed that foods such as wheat, corn, tomatoes, sugar, mushrooms, and dairy products were instrumental in producing behavioral disorders with this child.

Singh MM, Kay SR: Wheat gluten as a pathogenic factor in schizophrenia. Science 1976 Jan 30;191(4225):401-2.

Abstract:

Schizophrenics maintained on a cereal grain-free and milk-free diet and receiving optimal treatment with neuropleptics showed an interruption or reversal of their therapeutic progress during a period of "blind" wheat gluten challenge. The exacerbation of the disease process was not due to variations in neuroleptic doses. After termination of the gluten challenge, the course of improvement was reinstated. The observed effects seemed to be due to a primary schizophrenia-promoting effect of wheat gluten.

Dohan FC, Grasberger JC: Relapsed schizophrenics: earlier discharge from the hospital after cereal-free, milk-free diet. Am J Psychiatry. 1973 Jun;130(6):685-8. [No abstract available]

Goodwin MS, Cowen MA, Goodwin TC: Malabsorption and cerebral dysfunction: a multivariate and comparative study of autistic children. J Autism Child Schizophr 1971 Jan-Mar;1(1):48-62. [No abstract available]

Dohan FC: "Is celiac disease a clue to pathogenesis of schizophrenia?" Mental Hyg 1969; 53: 525-529. [No abstract available]

Dohan FC: Wheat "consumption" and hospital admissions for schizophrenia during World War II. A preliminary report. Am J Clin Nutr. 1966 Jan;18(1):7-10. [No abstract available]

Cooke WT, Smith WT: Neurological disorders associated with adult celiac disease. Brain 1966, 89: 683-722. [No abstract available]

Dohan FC: Cereals and schizophrenia: data and hypothesis. Acta Psychiat Scand 1966; 42: 125-152. [No abstract available]

updated 03/11/04

Journal articles regarding autism and gastrointestinal abnormalities

White JF.: Intestinal pathophysiology in autism. Exp Biol Med (Maywood). 2003 Jun;228(6):639-49.

Summary:

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Autism is a life-long developmental disorder affecting as many as 1 in 500 children. The causes for this profound disorder are largely unknown. Recent research has uncovered pathology in the gastrointestinal tract of autistic children. The pathology, reported to extend from the esophagus to the colon, is described here along with other studies pointing to a connection between diet and the severity of symptoms expressed in autism. The evidence that there is impaired intestinal permeability in autism is reviewed, and various theories are discussed by which a leaky gut could develop. Lastly, some possible ways in which impaired gastrointestinal function might influence brain function are discussed. FULL ARTICLE TEXT

Afzal N, Murch S, Thirrupathy K, Berger L, Fagbemi A, Heuschkel R: Constipation with acquired megarectum in children with autism. Pediatrics. 2003 Oct;112(4):939-42.

Centre for Pediatric Gastroenterology, Royal Free Hospital, Hampstead, London, United Kingdom.

OBJECTIVE: Recent evidence suggests that autistic children may have significant gastrointestinal symptoms. Although constipation occurs in 2% to 5% of healthy children, its clinical diagnosis is often difficult in children with behavioral disorders. We thus aimed to assess the prevalence of fecal loading in autistic children with gastrointestinal symptoms and to identify possible predictors of constipation. METHODS: We studied abdominal radiographs of 103 autistic children (87 boys) who were referred for gastroenterological assessment, in comparison with 29 control radiographs from children who were referred to the emergency department, most with abdominal pain. Radiographs were scored independently, in blinded manner, by 4 pediatric gastroenterologists and a radiologist. The severity of constipation was determined using a validated index. Details of stool habit, abdominal pain, dietary history, and laxative use were obtained from case notes. RESULTS: The incidence of constipation in the control subjects with abdominal pain was higher than reported for normal children. Despite this, moderate or severe constipation was more frequent in the autistic group than in the control subjects (36% vs 10%). Analysis of rectosigmoid loading showed more striking differences (54.4% of autistic children had moderate/severe loading or acquired megarectum compared with 24.1% of control subjects). Multivariate regression analysis showed consumption of milk to be the strongest predictor of constipation in the autistic group, whereas stool frequency, gluten consumption, soiling, and abdominal pain were not predictive of constipation. CONCLUSIONS: Constipation is a frequent finding in children with gastrointestinal symptoms and autism, particularly in the rectosigmoid colon, often with acquired megarectum. The absence of any correlation between the clinical history and the degree of fecal impaction in autistic children confirms the importance of an abdominal radiograph in the assessment of their degree of constipation.

FULL ARTICLE TEXT

Welch MG, Keune JD, Welch-Horan TB, Anwar N, Anwar M, Ruggiero DA.: Secretin activates visceral brain regions in the rat including areas abnormal in autism. Cell Mol Neurobiol. 2003 Oct;23(4-5):817-37.

Abstract:

Department of Psychiatry, Columbia University College of Physicians and Surgeons, NYSPI, 1051 Riverside Drive, New York, New York 10032, USA. mgw13@columbia.edu

1. The aim of this study was to determine whether central networks are involved in the presumptive behavioral and autonomic regulatory actions of secretin, a gut hormone that has been reported to have ameliorative effects in autistic children. 2. Central neural responses monitored by regional c-fos gene expression were examined in response to intracerebroventricular secretin injection in awake, freely-moving Sprague-Dawley rats. Tissue sections were incubated in an antibody to the c-fos gene product, Fos, and processed immunohistochemically. 3. Qualitative differences in Fos immunoreactivity in stress adaptation and visceral representation areas of the brain were observed between secretin- and vehicle-infused age-matched pairs (n = 4 pairs). Secretin-activated regions include the area postrema, dorsal motor nucleus, medial region of the nucleus of the solitary tract and its relay station in the lateral tegmentum, locus ceruleus, ventral periaqueductal gray, periventricular thalamic nucleus, paraventricular hypothalamus magnocellularis, medial and central amygdala, lateral septal complex as well as ependymal and subependymal nuclei lining the third ventricle. Specific areas of the cerebral cortex were heavily labeled in secretin-treated rats, as compared to controls: the medial bank of the anterior prefrontal cortex, orbitofrontal cortex, the piriform cortex. and the anterior olfactory nucleus. Secretin attenuated Fos immunoreactivity in the dorsal periaqueductal gray, intralaminar thalamus, medial parvicellular compartment of the hypothalamus, supraoptic nucleus of the hypothalamus, lateral amygdala, motor cortex, and the somatosensory and association areas of the parietal cortex. 4. Secretin alters the activity of structures involved in behavioral conditioning of stress adaptation and visceral reflex reactions. This study predicts a possible cellular mechanism, activation of third ventricular ependymal and subependymal cells, as well as central regulatory actions of secretin. The physiological effects of secretin on behavioral, endocrine, autonomic and sensory neuronal activation patterns, together, contribute to central c-fos activation. Secretin alters the activity of structures involved in behavioral conditioning of stress adaptation and visceral reflex reactions. This study predicts a possible cellular mechanism, activation of third ventricular ependymal and subependymal cells, as well as central regulatory actions of secretin. The physiological effects of secretin on behavioral, endocrine, autonomic and sensory neuronal activation patterns, together, contribute to central c-fos activation. **These findings mandate further investigation of secretin as a brain/gut stress regulatory hormone.**

Latcham F, Merino F, Lang A, Garvey J, Thomson MA, Walker-Smith JA, Davies SE, Phillips AD, Murch SH: A consistent pattern of minor immunodeficiency and subtle enteropathy in children with multiple food allergy. J Pediatr. 2003 Jul;143(1):39-47.

Centre for Paediatric Gastroenterology and Department of Dietetics and Histopathology, Royal Free and University College School of Medicine, London, United Kingdom.
OBJECTIVE: Although immunoglobulin (Ig)E-mediated allergies are readily identifiable, non-IgE-mediated allergies present more diagnostic difficulty. We performed a formal retrospective analysis to determine whether there is a recognizable clinical pattern in children. METHODS: We studied 121 children (mean age, 17.3 months) with multiple food allergies who were recruited on the basis of adequate immunological assessment by using case notes and parental questionnaire. RESULTS: Group 1 (n=44) had rapid reactions to dietary antigens, of whom 41 also showed delayed reactions. Group 2 (n=77) had delayed reactions only. Mean IgE was increased in group 1 but both groups otherwise shared a pattern of increased IgG1, decreased IgG2/4, and low-normal IgA. Lymphocyte subsets were skewed, with an increased percentage of CD4 and CD19 and decreased CD8 and natural killer cells. Gastroesophageal reflux, esophagitis, subtle enteropathy, and constipation were frequent in both groups. Of 55 exclusively breast-fed infants, 44 sensitized before weaning. Twenty-one of the mothers suffered from autoimmunity. CONCLUSIONS: There appears to be a recognizable pattern of immune deviation and minor enteropathy in children with multiple food allergy, irrespective of the speed of reactions. Disturbed gut motility is particularly common, as is a maternal history of autoimmunity. FULL ARTICLE TEXT

Molloy CA, Manning-Courtney P.: Prevalence of chronic gastrointestinal symptoms in children with autism and autistic spectrum disorders. Autism. 2003 Jun;7(2):165-71.

Abstract:

Center for Epidemiology and Biostatistics, Cincinnati Children's Hospital Medical Center, OH 45229-3039, USA. Cynthia.molloy@chmcc.org

The purpose of this study was to estimate the prevalence of chronic gastrointestinal symptoms in a general population of children with autism or autistic spectrum disorder (ASD). The study site was a clinic specializing in ASD in a large pediatric medical center serving a 10 county area in the midwestern USA. In a sample of 137 children, age 24-96 months, classified as having autism or ASD by the Autism Diagnostic Observation Schedule-Generic, 24 percent had a history of at least one chronic gastrointestinal symptom. The most common symptom was diarrhea, which occurred in 17 percent. There was no association between chronic gastrointestinal symptoms and a history of developmental regression. The potential phenotypic association between autism and gastrointestinal symptoms is discussed.

Buie T, Winter H, Kushak, R: Preliminary findings in gastrointestinal investigation of autistic patients. 2002.

Summary:

Harvard University and Mass General Hospital, http://www.ladders.org/autism.php

111 patients evaluated, ages 14 Months to 20 Years, all with GI symptoms of pain or diarrhea. Endoscopic findings: Esophagitis in 23 (20%), Gastritis in 14 (12%); 4 had Helicobacter pylori; Duodenitis in 11 (10%); 2 had Celiac Sprue; Eosinophilic Inflammation in 5 (5%). 10 out of 90 tested (11%) had unusually low enzyme activity: 2 with total pancreatic insufficiency and 5 with multiple enzyme defects. Lactase deficiency was found in 55% of ASD children tested, and combined deficiency of disacchraridase enzymes was found in 15%. Enzyme assays correlate well with hydrogen breath tests. Colitis was found in 11 of 89 patients (12%), none with features of Ulcerative Colitis or Crohn's. Histologic (biopsy reviewed) lymphoid nodular hyperplasia was found in 15 of 89 patients (16%). Eosinophilic inflammation was found in 13 of 89 patients (14%); cause or significance is unclear. Conclusions: more than 50% of autistic children appear to have GI symptoms, food allergies, and maldigestion or malabsorption issues. We need large, evidence-based studies need to be done in order to fully understand the gut-brain association in autism.

Krigsman, A, et al: Preliminary data presented at congressional hearing. 2002 Jun.

Summary:

New York University School of Medicine: www.med.nyu.edu

We examined 43 patients with autism, in whom we demonstrated enterocolitis in 65% and terminal ileal LNH in 90%. As of November, 2002, our total patient population now stands at 82, and the percentages of enterocolitis and LNH are essentially unchanged. Additional studies will follow.

Finegold SM, Molitoris D, Song Y, Liu C, Vaisanen ML, Bolte E, McTeague M, Sandler R, Wexler H, Marlowe EM, Collins MD, Lawson PA, Summanen P, Baysallar M, Tomzynski TJ, Read E, Johnson E, Rolfe R, Nasir P, Shah H, Haake DA, Manning P, Kaul A: Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis. 2002 Sep 1;35(Suppl 1):S6-S16.

Infectious Diseases Section, Veterans Affairs Medical Center, West Los Angeles, CA, USA. sidfinegol@aol.com

Some cases of late-onset (regressive) autism may involve abnormal flora because oral vancomycin, which is poorly absorbed, may lead to significant improvement in these children. Fecal flora of children with regressive autism was compared with that of control children, and clostridial counts were higher. The number of clostridial species found in the stools of children with autism was greater than in the stools of control children. Children with autism had 9 species of Clostridium not found in controls, whereas controls yielded only 3 species not found in children with autism. In all, there were 25 different clostridial species found. In gastric and duodenal specimens, the most striking finding was total absence of non-spore-forming anaerobes and microaerophilic bacteria from control children and significant numbers of such bacteria from children with autism. These studies demonstrate significant alterations in the upper and lower intestinal flora of children with late-onset autism and may provide insights into the nature of this disorder.

Wakefield AJ, Puleston JM, Montgomery SM, Anthony A, O'Leary JJ, Murch SH: Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. Aliment Pharmacol Ther 2002 Apr;16(4):663-74.

Abstract:

Inflammatory Bowel Disease Study Group, Centre for Gastroenterology, Department of Medicine, Royal Free and University College Medical School, London, UK. wakers@aol.com

There is growing awareness that primary gastrointestinal pathology may play an important role in the inception and clinical expression of some childhood developmental disorders, including autism. In addition to frequent gastrointestinal symptoms, children with autism often manifest complex biochemical and immunological abnormalities. The gut-brain axis is central to certain encephalopathies of extra-cranial origin, hepatic encephalopathy being the best characterized. Commonalities in the clinical characteristics of hepatic encephalopathy and a form of autism associated with developmental regression in an apparently previously normal child, accompanied by immune-mediated gastrointestinal pathology, have led to the proposal that there may be analogous mechanisms of toxic encephalopathy in patients with liver failure and some children with autism. Aberrations in opioid biochemistry are common to these two conditions, and there is evidence that opioid peptides may mediate certain aspects of the respective syndromes. The generation of plausible and testable hypotheses in this area may help to identify new treatment options in encephalopathies of extra-cranial origin. Therapeutic targets for this autistic phenotype may include: modification of diet and entero-colonic microbial milieu in order to reduce toxin substrates, improve nutritional status and modify mucosal immunity; anti-inflammatory/immunomodulatory therapy; and specific treatment of dysmotility, focusing, for example, on the pharmacology of local opioid activity in the gut.

Uhlmann V, Martin CM, Sheils O, Pilkington L, Silva I, Killalea A, Murch SB, Walker-Smith J, Thomson M, Wakefield AJ, O'Leary JJ: Potential viral pathogenic mechanism for new variant inflammatory bowel disease. Mol Pathol 2002 Apr;55(2):84-90

Abstract:

Department of Pathology, Coombe Women's Hospital, Dublin 8, Ireland .

AIMS: A new form of inflammatory bowel disease (ileocolonic lymphonodular hyperplasia) has been described in a cohort of children with developmental disorder. This study investigates the presence of persistent measles virus in the intestinal tissue of these patients (new variant inflammatory bowel disease) and a series of controls by molecular analysis. METHODS: Formalin fixed, paraffin wax embedded and fresh frozen biopsies from the terminal ileum were examined from affected children and histological normal controls. The measles virus Fusion (F) and Haemagglutinin (H) genes were detected by TaqMan reverse transcription polymerase chain reaction (RT-PCR) and the Nucleocapsid (N) gene by RT in situ PCR. Localisation of the mRNA signal was performed using a specific follicular dendritic cell antibody. RESULTS: Seventy five of 91 patients with a histologically confirmed diagnosis of ileal lymphonodular hyperplasia and enterocolitis were positive for measles virus in their intestinal tissue compared with five of 70 control patients. Measles virus was identified within the follicular dendritic cells and some lymphocytes in foci of reactive follicular hyperplasia. The copy number of measles virus ranged from one to 300,00 copies/ng total RNA. CONCLUSIONS: The data confirm an association between the presence of measles virus and gut pathology in children with developmental disorder.

Torrente F, Ashwood P, Day R, Machado N, Furlano RI, Anthony A, Davies SE, Wakefield AJ, Thomson MA, Walker-Smith JA, Murch SH: Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. Mol Psychiatry 2002;7(4):375-82, 334

Abstract:

Centre for Paediatric Gastroenterology, Royal Free & University College Medical School, London, UK .

We have reported lymphocytic colitis in children with regressive autism, with epithelial damage prominent. We now compare duodenal biopsies in 25 children with regressive autism to 11 with coeliac disease, five with cerebral palsy and mental retardation and 18 histologically normal controls. Immunohistochemistry was performed for lymphocyte and epithelial lineage and functional markers. We determined the density of intraepithelial and lamina propria lymphocyte populations, and studied mucosal immunoglobulin and complement C1q localisation. Standard histopathology showed increased enterocyte and Paneth cell numbers in the autistic children. Immunohistochemistry demonstrated increased lymphocyte infiltration in both epithelium and lamina propria with upregulated crypt cell proliferation, compared to normal and cerebral palsy controls. Intraepithelial lymphocytes and lamina propria plasma cells were lower than in coeliac disease, but lamina propria T cell populations were higher and crypt proliferation similar. Most strikingly, IgG deposition was seen on the basolateral epithelial surface in 23/25 autistic children, co-localising with complement C1q. This was not seen in the other conditions. These findings demonstrate a novel form of enteropathy in autistic children, in which increases in mucosal lymphocyte density and crypt cell proliferation occur with epithelial IgG deposition. The features are suggestive of an autoimmune lesion.

Wakefield AJ, Puleston JM, Montgomery SM, Anthony A, O'Leary JJ, Murch SH: Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. Aliment Pharmacol Ther. 2002 Apr;16(4):663-74.

Inflammatory Bowel Disease Study Group, Centre for Gastroenterology, Department of Medicine, Royal Free and University College Medical School, London, UK. wakers@aol.com

There is growing awareness that primary gastrointestinal pathology may play an important role in the inception and clinical expression of some childhood developmental disorders, including autism. In addition to frequent gastrointestinal symptoms, children with autism often manifest complex biochemical and immunological abnormalities. The gut-brain axis is central to certain encephalopathies of extra-cranial origin, hepatic encephalopathy being the best characterized. Commonalities in the clinical characteristics of hepatic encephalopathy and a form of autism associated with developmental regression in an apparently previously normal child, accompanied by immune-mediated gastrointestinal pathology, have led to the proposal that there may be analogous mechanisms of toxic encephalopathy in patients with liver failure and some children with autism. Aberrations in opioid biochemistry are common to these two conditions, and there is evidence that opioid peptides may mediate certain aspects of the respective syndromes. The generation of plausible and testable hypotheses in this area may help to identify new treatment options in encephalopathies of extra-cranial origin. Therapeutic targets for this autistic phenotype may include: modification of diet and entero-colonic microbial milieu in order to reduce toxin substrates, improve nutritional status and modify mucosal immunity; anti-inflammatory/immunomodulatory therapy; and specific treatment of dysmotility, focusing, for example, on the pharmacology of local opioid activity in the gut. FULL ARTICLE TEXT

Furlano RI, Anthony A, Day R, Brown A, McGarvey L, Thomson MA, Davies SE, Berelowitz M, Forbes A, Wakefield AJ, Walker-Smith JA, Murch SH: Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. J Pediatr 2001 Mar;138(3):366-72.

Abstract:

University Department of Paediatric Gastroenterology, the Inflammatory Bowel Diseases Study Group, Royal Free and University College School of Medicine, London, United Kingdom.

OBJECTIVES: We have reported colitis with ileal lymphoid nodular hyperplasia (LNH) in children with regressive autism. The aims of this study were to characterize this lesion and determine whether LNH is specific for autism. METHODS: Ileo-colonoscopy was performed in 21 consecutively evaluated children with autistic spectrum disorders and bowel symptoms. Blinded comparison was made with 8 children with histologically normal ileum and colon, 10 developmentally normal children with ileal LNH, 15 with Crohn's disease, and 14 with ulcerative colitis. Immunohistochemistry was performed for cell lineage and functional markers, and histochemistry was performed for glycosaminoglycans and basement membrane thickness. RESULTS: Histology demonstrated lymphocytic colitis in the autistic children, less severe than classical inflammatory bowel disease. However, basement membrane thickness and mucosal gamma delta cell density were significantly increased above those of all other groups including patients with inflammatory bowel disease. CD8(+) density and intraepithelial lymphocyte numbers were higher than those in the Crohn's disease, LNH, and normal control groups; and CD3 and plasma cell density and crypt proliferation were higher than those in normal and LNH control groups. Epithelial, but not lamina propria, glycosaminoglycans were disrupted. However, the epithelium was HLA-DR(-), suggesting a predominantly T(H)2 response. INTERPRETATION: Immunohistochemistry confirms a distinct lymphocytic colitis in autistic spectrum disorders in which the epithelium appears particularly affected. This is consistent with increasing evidence for gut epithelial dysfunction in autism.

Wakefield AJ, Anthony A, Murch SH, Thomson M, Montgomery SM, Davies S, O'Leary JJ, Berelowitz M, Walker-Smith JA: Enterocolitis in children with developmental disorders. Am J Gastroenterol. 2000 Sep;95(9):2285-95. University Department of Medicine, Royal Free and University College Medical School, London, United Kingdom.
OBJECTIVE: Intestinal pathology, i.e., ileocolonic lymphoid nodular hyperplasia (LNH) and mucosal inflammation, has been described in children with developmental disorders. This study describes some of the endoscopic and pathological characteristics in a group of children with developmental disorders (affected children) that are associated with behavioral regression and bowel symptoms, and compares them with pediatric controls. METHODS: Ileocolonoscopy and biopsy were performed on 60 affected children (median age 6 yr, range 3-16; 53 male). Developmental diagnoses were autism (50 patients), Asperger's syndrome (five), disintegrative disorder (two), attention deficit hyperactivity disorder (ADHD) (one), schizophrenia (one), and dyslexia (one). Severity of ileal LNH was graded (0-3) in both affected children and 37 developmentally normal controls (median age 11 yr, range 2-13 yr) who were investigated for possible inflammatory bowel disease (IBD). Tissue sections were reviewed by three pathologists and scored on a standard proforma. Data were compared with ileocolonic biopsies from 22 histologically normal children (controls) and 20 children with ulcerative colitis (UC), scored in an identical manner. Gut pathogens were sought routinely. RESULTS: Ileal LNH was present in 54 of 58 (93%) affected children and in five of 35 (14.3%) controls ($p < 0.001$). Colonic LNH was present in 18 of 60 (30%) affected children and in two of 37 (5.4%) controls ($p < 0.01$). Histologically, reactive follicular hyperplasia was present in 46 of 52 (88.5%) ileal biopsies from affected children and in four of 14 (29%) with UC, but not in non-IBD controls ($p < 0.01$). Active ileitis was present in four of 51 (8%) affected children but not in controls. Chronic colitis was identified in 53 of 60 (88%) affected children compared with one of 22 (4.5%) controls and in 20 of 20 (100%) with UC. Scores of frequency and severity of inflammation were significantly greater in both affected children and those with UC, compared with controls ($p < 0.001$). CONCLUSIONS: A new variant of inflammatory bowel disease is present in this group of children with developmental disorders. FULL ARTICLE TEXT

Sandler RH, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, Vaisanen ML, Nelson MN, Wexler HM: Short-term benefit from oral vancomycin treatment of regressive-onset autism. J Child Neurol. 2000 Jul;15(7):429-35.

Section of Pediatric Gastroenterology and Nutrition, Rush Children's Hospital, Rush Medical College, Chicago, IL 60612, USA. rushstudy@aol.com

In most cases symptoms of autism begin in early infancy. However, a subset of children appears to develop normally until a clear deterioration is observed. Many parents of children with "regressive"-onset autism have noted antecedent antibiotic exposure followed by chronic diarrhea. We speculated that, in a subgroup of children, disruption of indigenous gut flora might promote colonization by one or more neurotoxin-producing bacteria, contributing, at least in part, to their autistic symptomatology. To help test this hypothesis, 11 children with regressive-onset autism were recruited for an intervention trial using a minimally absorbed oral antibiotic. Entry criteria included antecedent broad-spectrum antimicrobial exposure followed by chronic persistent diarrhea, deterioration of previously acquired skills, and then autistic features. Short-term improvement was noted using multiple pre- and post-therapy evaluations. These included coded, paired videotapes scored by a clinical psychologist blinded to treatment status; these noted improvement in 8 of 10 children studied. Unfortunately, these gains had largely waned at follow-up. Although the protocol used is not suggested as useful therapy, these results indicate that a possible gut flora-brain connection warrants further investigation, as it might lead to greater pathophysiologic insight and meaningful prevention or treatment in a subset of children with autism.

Kawashima H, Mori T, Kashiwagi Y, Takekuma K, Hoshika A, Wakefield A: Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism. Dig Dis Sci 2000 Apr;45(4):723-9.

Abstract:

Department of Paediatrics, Tokyo Medical University, Japan .

It has been reported that measles virus may be present in the intestine of patients with Crohn's disease. Additionally, a new syndrome has been reported in children with autism who exhibited developmental regression and gastrointestinal symptoms (autistic enterocolitis), in some cases soon after MMR vaccine. It is not known whether the virus, if confirmed to be present in these patients, derives from either wild strains or vaccine strains. In order to characterize the strains that may be present, we have carried out the detection of measles genomic RNA in peripheral mononuclear cells (PBMC) in eight patients with Crohn's disease, three patients with ulcerative colitis, and nine children with autistic enterocolitis. As controls, we examined healthy children and patients with SSPE, SLE, HIV-1 (a total of eight cases). RNA was purified from PBMC by Ficoll-paque, followed by reverse transcription using AMV; cDNAs were subjected to nested PCR for detection of specific regions of the hemagglutinin (H) and fusion (F) gene regions. Positive samples were sequenced directly, in nucleotides 8393-8676 (H region) or 5325-5465 (from noncoding F to coding F region). One of eight patients with Crohn disease, one of three patients with ulcerative colitis, and three of nine children with autism, were positive. Controls were all negative. The sequences obtained from the patients with Crohn's disease shared the characteristics with wild-strain virus. The sequences obtained from the patients with ulcerative colitis and children with autism were consistent with being vaccine strains. The results were concordant with the exposure history of the patients. Persistence of measles virus was confirmed in PBMC in some patients with chronic intestinal inflammation.

Horvath K, Papadimitriou JC, Rabsztyn A, Drachenberg C, Tildon JT: Gastrointestinal abnormalities in children with autistic disorder. J Pediatr 1999 Nov;135(5):559-63

Abstract:

Department of Pediatrics, University of Maryland School of Medicine, Baltimore , USA .

OBJECTIVES: Our aim was to evaluate the structure and function of the upper gastrointestinal tract in a group of patients with autism who had gastrointestinal symptoms. STUDY DESIGN: Thirty-six children (age: 5.7 +/- 2 years, mean +/- SD) with autistic disorder underwent upper gastrointestinal endoscopy with biopsies, intestinal and pancreatic enzyme analyses, and bacterial and fungal cultures. The most frequent gastrointestinal complaints were chronic diarrhea, gaseousness, and abdominal discomfort and distension. RESULTS: Histologic examination in these 36 children revealed grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15, and chronic duodenitis in 24. The number of Paneth's cells in the duodenal crypts was significantly elevated in autistic children compared with non-autistic control subjects. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function. Seventy-five percent of the autistic children (27/36) had an increased pancreatico-biliary fluid output after intravenous secretin administration. Nineteen of the 21 patients with diarrhea had significantly higher fluid output than those without diarrhea. CONCLUSIONS: Unrecognized gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioral problems of the non-verbal autistic patients. The observed increase in pancreatico-biliary secretion after secretin infusion suggests an upregulation of secretin receptors in the pancreas and liver. Further studies are required to determine the possible association between the brain and gastrointestinal dysfunctions in children with autistic disorder.

Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998 Feb 28;351(9103): 637-41

Abstract:

Inflammatory Bowel Disease Study Group, University Department of Medicine, Royal Free Hospital and School of Medicine, London, UK .

BACKGROUND: We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder. METHODS: 12 children (mean age 6 years [range 3-10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined. FINDINGS: Onset of behavioural symptoms was associated, by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in the colon in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative

psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and MRI and EEG tests were normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls (p=0.003), low haemoglobin in four children, and a low serum IgA in four children. INTERPRETATION: We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

D'Eufemia P., Celli M., Finocchiaro R., Pacifico L., Viozzi L., Zaccagnini M., Cardi E., Giardini O: Abnormal Intestinal Permeability in Children with Autism. Acta Paediatrica,1996; 85: 1076-1079.

Abstract:

Institute of Pediatrics, La Sapienza University of Rome , Italy .

We determined the occurrence of gut mucosal damage using the intestinal permeability test in 21 autistic children who had no clinical and laboratory findings consistent with known intestinal disorders. An altered intestinal permeability was found in 9 of the 21 (43%) autistic patients, but in none of the 40 controls. Compared to the controls, these nine patients showed a similar mean mannitol recovery, but a significantly higher mean lactulose recovery (1.64% +/- 1.43 vs 0.38% +/- 0.14; P < 0.001). **We speculate that an altered intestinal permeability could represent a possible mechanism for the increased passage through the gut mucosa of peptides derived from foods with subsequent behavioural abnormalities.**

updated 03/11/04

Selection of journal articles regarding immune dysfunction and/or mercury toxicity in autism

J. Van de Water, P. Ashwood, R. Hansen, B. Goodlin-Jones, K. Lam, and M.E. Gershwin. Reduced IgG Response to Common Vaccine Antigens for Patients with Autism Spectrum Disorder (ASD); May, 2004.
Summary:

Internal Medicine and M.I.N.D. Institute, UC Davis, Davis, CA 95616.

There is a growing awareness of an immunological involvement in some ASD children. To better define the immune status of children with ASD, we examined by ELISA the serologic response of patients and age-matched typically developing (TD) controls to common vaccine antigens. These included Bordetella, Diptheria, Tetanus, Measles, Mumps and Rubella. All children analyzed were vaccinated with DTaP and MMR. Based on vaccination schedules, comparisons were made between patients and controls in three age groups: 2-5 yrs, 5-8 yrs and 8-14 yrs.

The most striking differences were observed in the 2-5 age group where patients with ASD had a significantly lower IgG response to Bordetella (p = 0.0003), Diptheria (p = 0.006), and Mumps (p = 0.043) than TD controls. There was also a trend for a lower IgG responses against Measles and Tetanus in the ASD group. In the 5-8 age group, there were no differences in the response to any of the test antigens. In the over 8 age group, while there was a trend towards lower IgG responses to Bordetella, Tetanus and Mumps antigens, only the IgG response to Measles was significantly reduced (p = 0.016). Interestingly, the response to Rubella was equal in groups over time. Finally, at no time point did the median of the response of the ASD group exceed that of the TD population. In conclusion, all patients with ASD were immunopositive for the vaccine antigens tested, their responses were significantly lower than the TD controls suggesting an immune dysregulation in these children.

Vojdani A, Pangborn JB, Vojdani E, Cooper EL.: Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism. Int J Immunopathol Pharmacol. 2003 Sep-Dec;16(3):189-99.

Abstract:
Lab. Comparative Immunology, Dept. Neurobiology, UCLA Medical Center, Los Angeles, CA, USA.

Similar to many complex autoimmune diseases, genetic and environmental factors including diet, infection and xenobiotics play a critical role in the development of autism. In this study, we postulated that infectious agent antigens such as streptokinase, dietary peptides (gliadin and casein) and ethyl mercury (xenobiotic) bind to different lymphocyte receptors and tissue enzyme (DPP IV or CD26). We assessed this hypothesis first by measuring IgG, IgM and IgA antibodies against CD26, CD69, streptokinase (SK), gliadin and casein peptides and against ethyl mercury bound to human serum albumin in patients with autism. A significant percentage of children with autism developed anti-SK, anti-gliadin and casein peptides and anti-ethyl mercury antibodies, concomitant with the appearance of anti-CD26 and anti-CD69 autoantibodies. These antibodies are synthesized as a result of SK, gliadin, casein and ethyl mercury binding to CD26 and CD69, indicating that they are specific. Immune absorption demonstrated that only specific antigens, like CD26, were capable of significantly reducing serum anti-CD26 levels. However, for direct demonstration of SK, gliadin, casein and ethyl mercury to CD26 or CD69, microtiter wells were coated with CD26 or CD69 alone or in combination with SK, gliadin, casein or ethyl mercury and then reacted with enzyme labeled rabbit anti-CD26 or anti-CD69. Adding these molecules to CD26 or CD69 resulted in 28-86% inhibition of CD26 or CD69 binding to anti-CD26 or anti-CD69 antibodies. The highest % binding of these antigens or peptides to CD26 or CD69 was attributed to SK and the lowest to casein peptides. We, therefore, propose that bacterial antigens (SK), dietary peptides (gliadin, casein) and Thimerosal (ethyl mercury) in individuals with pre-disposing HLA molecules, bind to CD26 or CD69 and induce antibodies against these molecules. In conclusion, this study is apparently the first to demonstrate that dietary peptides, bacterial toxins and xenobiotics bind to lymphocyte receptors and/or tissue enzymes, resulting in autoimmune reaction in children with autism.

Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougle CJ.: Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. Pediatrics. 2003 Nov;112(5):e420.

Summary:

Department of Psychiatry, Indiana University School of Medicine, and James Whitcomb Riley Hospital for Children Indianapolis 46202-4800, USA.

OBJECTIVES: Increased prevalence of familial autoimmune disease is a common finding among probands with various autoimmune disorders. Autistic disorder (autism) is a highly genetic disorder with known immune and immunogenetic abnormalities. Previous research has found an increased frequency of autoimmune disorders in families with autistic probands. We further investigated this association by determining the frequency of autoimmune disorders in families that have probands with pervasive developmental disorders (PDDs), including autism, compared with 2 control groups. METHODS: Three well-defined study groups, including 1) families that have a child with a PDD, 2) families that have a child with an autoimmune disorder, and 3) families with a healthy control child, constituted the sample. A questionnaire inquiring about which first- and second-degree family members had received a diagnosis of having specific autoimmune disorders was completed by 101 families in each group. RESULTS: The frequency of autoimmune disorders was significantly higher in families of the PDD probands compared with families of both the autoimmune and healthy control probands. Autoimmunity was highest among the parents of PDD probands compared with parents of the healthy control subjects. Hypothyroidism/Hashimoto's thyroiditis and rheumatic fever were significantly more common in families with PDD probands than in the healthy control families. CONCLUSIONS: Autoimmunity was increased significantly in families with PDD compared with those of healthy and autoimmune control subjects. These preliminary findings warrant additional investigation into immune and autoimmune mechanisms in autism.

Singh VK, Jensen RL.: Elevated levels of measles antibodies in children with autism. Pediatr Neurol. 2003 Apr;28(4):292-4.

Abstract:
Department of Biology and Biotechnology Center, Utah State University, Logan, Utah, USA.
Virus-induced autoimmunity may play a causal role in autism. To examine the etiologic link of viruses in this brain disorder, we conducted a serologic study of measles virus, mumps virus, and rubella virus. Viral antibodies were measured by enzyme-linked immunosorbent assay in the serum of autistic children, normal children, and siblings of autistic children. The level of measles antibody, but not mumps or rubella antibodies, was significantly higher in autistic children as compared with normal children (P = 0.003) or siblings of autistic children (P < virus or strain vaccine the to reaction immune abnormal an of sign a be might infection measles type wild absence in which virus, response hyperimmune have children autistic Thus children. siblings normal not but 83% found was antigen this antibody The weight. molecular kd 74 approximately protein against directed that revealed immunoblotting Furthermore, 0.0001).>

Lipkin WI, Hornig M.: Microbiology and immunology of autism spectrum disorders. Novartis Found Symp. 2003;251:129-43; discussion 144-8, 281-97.

Abstract:
Center for Immunopathogenesis and Infections Diseases, Mailman School of Public Health, Columbia University, 722 West 168th Street, New York, NY 10032, USA.
Both generic and environmental factors are likely to contribute to the pathogenesis of neurodevelopmental disorders. Even in heritable disorders of high penetrance, variability in timing of onset or severity of disease indicate a role for modifying principles. Investigation in animal models of the consequences of interactions between host response genes and microbes, toxins, and other environmental agents in a temporal context may elucidate the pathophysiology of a wide spectrum of chronic diseases. Here we 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 plans for translational research in animal models and prospective human birth cohorts.

Holmes AS, Blaxill MF, Haley BE.: Reduced levels of mercury in first baby haircuts of autistic children. Int J Toxicol. 2003 Jul-Aug;22(4):277-85.

Abstract:
SafeMinds, Cambridge, Massachusetts, USA.
Reported rates of autism have increased sharply in the United States and the United Kingdom. One possible factor underlying these increases is increased exposure to mercury through thimerosal-containing vaccines, but vaccine exposures need to be evaluated in the context of cumulative exposures during gestation and early infancy. Differential rates of postnatal mercury elimination may explain why similar gestational and infant exposures produce variable neurological effects. First baby haircut samples were obtained from 94 children diagnosed with autism using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) criteria and 45 age- and gender-matched controls. Information on diet, dental amalgam fillings, vaccine history, Rho D immunoglobulin administration, and autism symptom severity was collected through a maternal survey questionnaire and clinical observation. Hair mercury levels in the autistic group were 0.47 ppm versus 3.63 ppm in controls, a significant difference. The mothers in the autistic group had significantly

higher levels of mercury exposure through Rho D immunoglobulin injections and amalgam fillings than control mothers. Within the autistic group, hair mercury levels varied significantly across mildly, moderately, and severely autistic children, with mean group levels of 0.79, 0.46, and 0.21 ppm, respectively. Hair mercury levels among controls were significantly correlated with the number of the mothers' amalgam fillings and their fish consumption as well as exposure to mercury through childhood vaccines, correlations that were absent in the autistic group. Hair excretion patterns among autistic infants were significantly reduced relative to control. These data cast doubt on the efficacy of traditional hair analysis as a measure of total mercury exposure in a subset of the population. In light of the biological plausibility of mercury's role in neurodevelopmental disorders, the present study provides further insight into one possible mechanism by which early mercury exposures could increase the risk of autism.

Geier DA, Geier MR.: An assessment of the impact of thimerosal on childhood neurodevelopmental disorders. Pediatr Rehabil. 2003 Apr-Jun;6(2):97-102.

Abstract:
The Genetic Centers of America, 14 Redgate Court, Silver Spring, MD 20905, USA.

The prevalence of autism in the US has risen from 1 in approximately 2500 in the mid-1980s to 1 in approximately 300 children in the mid-1990s. The purpose of this study was to evaluate whether mercury from thimerosal in childhood vaccines contributed to neurodevelopmental disorders. Neurodevelopmental disorder dose-response curves for increasing mercury doses of thimerosal in childhood vaccines were determined based upon examination of the Vaccine Adverse Events Reporting System (VAERS) database and the 2001 US' Department of Education Report. The instantaneous dosage of mercury children received in comparison to the Food and Drug Administration (FDA)'s maximum permissible dose for the oral ingestion of methylmercury was also determined. The dose-response curves showed increases in odds ratios of neurodevelopmental disorders from both the VAERS and US Department of Education data closely linearly correlated with increasing doses of mercury from thimerosal-containing childhood vaccines and that for overall odds ratios statistical significance was achieved. Similar slopes and linear regression coefficients for autism odds ratios in VAERS and the US Department of Education data help to mutually validate each other. Controls employed in the VAERS and US Department of Education data showed minimal biases. The evidence presented here shows that the occurrence of neurodevelopmental disorders following thimerosal-containing childhood vaccines does not appear to be coincidental.

Singh VK, Lin SX, Newell E, Nelson C., Abnormal measles-mumps-rubella antibodies and CNS autoimmunity in children with autism. J Biomed Sci 2002 Jul-Aug;9(4):359-64.

Abstract:

Department of Biology and Biotechnology Center, Utah State University, Logan, Utah, USA .

Autoimmunity to the central nervous system (CNS), especially to myelin basic protein (MBP), may play a causal role in autism, a neurodevelopmental disorder. Because many autistic children harbor elevated levels of measles antibodies, we conducted a serological study of measles-mumps-rubella (MMR) and MBP autoantibodies. Using serum samples of 125 autistic children and 92 control children, antibodies were assayed by ELISA or immunoblotting methods. ELISA analysis showed a significant increase in the level of MMR antibodies in autistic children. Immunoblotting analysis revealed the presence of an unusual MMR antibody in 75 of 125 (60%) autistic sera but not in control sera. This antibody specifically detected a protein of 73-75 kD of MMR. This protein band, as analyzed with monoclonal antibodies, was immunopositive for measles hemagglutinin (HA) protein but not for measles nucleoprotein and rubella or mumps viral proteins. Thus the MMR antibody in autistic sera detected measles HA protein, which is unique to the measles subunit of the vaccine. Furthermore, over 90% of MMR antibody-positive autistic sera were also positive for MBP autoantibodies, suggesting a strong association between MMR and CNS autoimmunity in autism. Stemming from this evidence, we suggest that an inappropriate antibody response to MMR, specifically the measles component thereof, might be related to pathogenesis of autism.

Korvatska E, Van de Water J, Anders TF, Gershwin ME: Genetic and immunologic considerations in autism. Neurobiol Dis 2002 Mar;9(2):107-25.

Abstract:

Division of Rheumatology, Allergy, and Clinical Immunology, University of California at Davis, Davis, California 95616, USA .

According to recent epidemiological surveys, autistic spectrum disorders have become recognized as common childhood psychopathologies. These life-lasting conditions demonstrate a strong genetic determinant consistent with a polygenic mode of inheritance for which several autism susceptibility regions have been identified. Parallel evidence of immune abnormalities in autistic patients argues for an implication of the immune system in pathogenesis. This review summarizes advances in the molecular genetics of autism, as well as recently emerging concerns addressing the disease incidence and triggering factors. The neurochemical and immunologic findings are analyzed in the context of a neuroimmune hypothesis for autism. Studies of disorders with established neuroimmune nature indicate multiple pathways of the pathogenesis; herein, we discuss evidence of similar phenomena in autism.

Croonenberghs J, Bosmans E, Deboutte D, Kenis G, Maes M: Activation of the inflammatory response system in autism. Neuropsychobiology 2002;45(1):1-6.

Abstract:

University Center of Child and Adolescent Psychiatry, Antwerp, Belgium .

BACKGROUND/AIM: There is now some evidence that autism may be accompanied by abnormalities in the inflammatory response system (IRS). Products of the IRS, such as proinflammatory cytokines, may induce some of the behavioral symptoms of autism, such as social withdrawal, resistance to novelty and sleep disturbances. The main aim of the present study was to examine whether autism is accompanied by an activation of the IRS. METHODS: We measured the production of interleukin (IL)-6, IL-10, the IL-1 receptor antagonist (IL-1RA), interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha by whole blood and the serum concentrations of IL-6, the IL-2 receptor (IL-2R) and IL-1RA. RESULTS: This study showed a significantly increased production of IFN-gamma and IL-1RA and a trend toward a significantly increased production of IL-6 and TNF-alpha by whole blood of autistic children. There were no significant differences in the serum concentrations of IL-6, IL-2R and IL-1RA between autistic and normal children. CONCLUSIONS: These results suggest that autism may be accompanied by an activation of the monocytic (increased IL-1RA) and Th-1-like (increased IFN-gamma) arm of the IRS. It is hypothesized that increased production of proinflammatory cytokines could play a role in the pathophysiology of autism.

Malek-Ahmadi P: Cytokines and etiopathogenesis of pervasive developmental disorders. Med Hypotheses 2001 Mar;56(3):321-4.

Abstract:

Department of Neuropsychiatry, School of Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas 79430, USA .

Autistic disorder, also known as early infantile autism, is a developmental disorder of unknown etiology. However, there is some evidence to suggest that abnormalities of the immune system mediate the pathophysiology of autistic disorder. Cytokines, which play a pivotal role in initiating and maintaining immune responses, have been implicated in the etiopathogenesis of major neuropsychiatric disorders including autism. Cytokines are synthesized in the periphery, as well as in the central nervous system, and exert their effects by binding to their receptors in the nervous tissues. It is suggested that, in genetically predisposed individuals, overproduction or decreased synthesis of certain cytokines may result in neurodevelopmental arrest and/or neurotoxicity.

Jyonouchi H, Sun S, Le H.: Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression. J Neuroimmunol 2001 Nov 1;120(1-2):170-9

Abstract:

Department of Pediatrics, University of Minnesota , MMC 610 FUMC, 420 Delaware Street SE, Minneapolis, MN 55455, USA . jyono001@tc.umn.edu

We determined innate and adaptive immune responses in children with developmental regression and autism spectrum disorders (ASD, N=71), developmentally normal siblings (N=23), and controls (N=17). With lipopolysaccharide (LPS), a stimulant for innate immunity, peripheral blood mononuclear cells (PBMCs) from 59/71 (83.1%) ASD patients produced >2 SD above the control mean (CM) values of TNF-alpha, IL-1beta, and/or IL-6 produced by control PBMCs. ASD PBMCs produced higher levels of proinflammatory/counter-regulatory cytokines without stimuli than controls. With stimulants of phytohemagglutinin (PHA), tetanus, IL-12p70, and IL-18, PBMCs from 47.9% to 60% of ASD patients produced >2 SD above the CM values of TNF-alpha depending on stimulants. Our results indicate excessive innate immune responses in a number of ASD children that may be most evident in TNF-alpha production.

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(2):76-84.

Abstract:

Department of Pediatrics, University of Minnesota , Minneapolis, Minn., USA .

Objectives: Children with autism spectrum disorder (ASD) frequently reveal various gastrointestinal (GI) symptoms that may resolve with an elimination diet along with apparent improvement of some of the behavioral symptoms. Evidence suggests that ASD may be accompanied by aberrant (inflammatory) innate immune responses. This may predispose ASD children to sensitization to common dietary proteins (DP), leading to GI inflammation and aggravation of some behavioral symptoms. Methods: We measured IFN-gamma, IL-5, and TNF-alpha production against representative DPs [gliadin, cow's milk protein (CMP), and soy] by peripheral blood mononuclear cells (PBMCs) from ASD and control children [those with DP intolerance (DPI), ASD siblings, and healthy unrelated children]. We evaluated the results in association with proinflammatory and counter-regulatory cytokine production with endotoxin (LPS), a microbial product of intestinal flora and a surrogate stimulant for innate immune responses. Results: ASD PBMCs produced elevated IFN-gamma and TNF-alpha, but not IL-5 with common DPs at high frequency as observed in DPI PBMCs. ASD PBMCs revealed increased proinflammatory cytokine responses with LPS at high frequency with positive correlation between proinflammatory cytokine production with LPS and IFN-gamma and TNF-alpha production against DPs. Such correlation was less evident in DPI PBMCs. Conclusion: Immune reactivity to DPs may be associated with apparent DPI and GI inflammation in ASD children that may be partly associated with aberrant innate immune response against endotoxin, a product of the gut bacteria.

Hornig M, Lipkin WI: Infectious and immune factors in the pathogenesis of neurodevelopmental disorders: epidemiology, hypotheses, and animal models. Ment Retard Dev Disabil Res Rev 2001;7(3):200-10.

Abstract:

Emerging Diseases Laboratory, Gillespie Neuroscience Research Facility, University of California , Irvine, California 92697-4292, USA . mhornig@uci.edu

Both genetic and environmental factors contribute to the pathogenesis of a wide variety of neurodevelopmental disorders, including autism, mental retardation, and schizophrenia. Some heritable disorders approach 100% penetrance; nonetheless, even in these disorders, subtle aspects of clinical disease expression may be influenced by the environment. 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.

Bernard S, Enayati A, Redwood L, Roger H, Binstock T: Autism: a novel form of mercury poisoning. Med Hypotheses 2001 Apr;56(4):462-71.

Abstract:

ARC Research, Cranford, New Jersey 07901, USA .

Autism is a syndrome characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movements, and sensory dysfunction. Recent epidemiological studies suggest that autism may affect 1 in 150 US children. Exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism, and the similarities extend to neuroanatomy, neurotransmitters, and biochemistry. Thimerosal, a preservative added to many vaccines, has become a major source of mercury in children who, within their first two years, may have received a quantity of mercury that exceeds safety guidelines. A review of medical literature and US government data suggests that: (i) many cases of idiopathic autism are induced by early mercury exposure from thimerosal; (ii) this type of autism represents an unrecognized mercurial syndrome; and (iii) genetic and non-genetic factors establish a predisposition whereby thimerosal's adverse effects occur only in some children.

Persico AM, Militerni R, Bravaccio C, Schneider C, Melmed R, Trillo S, Montecchi F, Palermo MT, Pascucci T, Puglisi-Allegra S, Reichelt KL, Conciatori M, Baldi A, Keller F: Adenosine deaminase alleles and autistic disorder: case-control and family-based association studies. Am J Med Genet 2000 Dec 4;96(6):784-90.

Abstract:

Laboratory of Neuroscience, Department of Physiology and Neuroscience, Libera Universita Campus Bio-Medico, Rome, Italy .

Adenosine deaminase (ADA) plays a relevant role in purine metabolism, immune responses, and peptidase activity, which may be altered in some autistic patients. Codominant ADA1 and ADA2 alleles code for ADA1 and ADA2 allozymes, the most frequent protein isoforms in the general population. Individuals carrying one copy of the ADA2 allele display 15 to 20% lower catalytic activity compared to ADA1 homozygotes. Recent preliminary data suggest that ADA2 alleles may be more frequent among autistic patients than healthy controls. The present study was undertaken to replicate these findings in a new case-control study, to test for linkage/association using a family-based design, and to characterize ADA2-carrying patients by serotonin blood levels, peptiduria, and head circumference. ADA2 alleles were significantly more frequent in 91 Caucasian autistic patients of Italian descent than in 152 unaffected controls (17.6% vs. 7.9%, P = 0.018), as well as among their fathers. Family-based tests involving these 91 singleton families, as well as 44 additional Caucasian-American trios, did not support significant linkage/association. However, the observed preferential maternal transmission of ADA2 alleles, if replicated, may point toward linkage disequilibrium between the ADA2 polymorphism and an imprinted gene variant located in its vicinity. Racial and ethnic differences in ADA allelic distributions, together with the low frequency of the ADA2 allele, may pose methodological problems to future linkage/association studies. Direct assessments of ADA catalytic activity in autistic individuals and unaffected siblings carrying ADA1/ADA1 vs ADA1/ADA2 genotypes may provide stronger evidence of ADA2 contributions to autistic disorder.

Megson MN: Is autism a G-alpha protein defect reversible with natural vitamin A? Med Hypotheses 2000 Jun;54(6):979-83.

Abstract:

Pediatric and Adolescent Ability Center, Richmond, VA 23226, USA .

Autism may be a disorder linked to the disruption of the G-alpha protein, affecting retinoid receptors in the brain. A study of 60 autistic children suggests that autism may be caused by inserting a G-alpha protein defect, the pertussis toxin found in the DPT vaccine, into genetically at-risk children. This toxin separates the G-alpha protein from retinoid receptors. Those most at risk report a family history of at least one parent with a pre-existing G-alpha protein defect, including night blindness, pseudohypoparathyroidism or adenoma of the thyroid or pituitary gland.Natural vitamin A may reconnect the retinoid receptors critical for vision, sensory perception, language processing and attention. Autism spectrum disorders have increased from 1 in 10 000 in 1978 to 1 in 300 in some US communities in 1999. Recent evidence indicates that autism is a disorder of the nervous system and the immune system, affecting multiple metabolic pathways.

Gupta S: Immunological treatments for autism. J Autism Dev Disord 2000 Oct;30(5):475-9.

Abstract:

Division of Basic and Clinical Immunology, Medical Sciences I, University of California , Irvine 92697, USA . sgupta@uci.edu

Several investigators, including ourselves, have reported significant changes in various immune responses in children with autism. These changes demonstrate dysregulation of the immune system (deficiency in some components of the immune system and excesses in others). In addition, certain genes in the major histocompatibility complex (that regulates immune responses) appear to be involved in autism. Based upon immunological abnormalities, various treatment modalities have been applied to children with autism. In this brief review, these immunological changes and various biological therapies are analyzed and summarized.

Hornig M, Weissenbock H, Horscroft N, Lipkin WI: An infection-based model of neurodevelopmental damage. Proc Natl Acad Sci USA 1999 Oct 12; 96(21):12102-7.

Abstract:

Emerging Diseases Laboratory, Department of Microbiology, University of California , Irvine, CA 92697-4292, USA .

Perinatal exposure to infectious agents and toxins is linked to the pathogenesis of neuropsychiatric disorders, but the mechanisms by which environmental triggers interact with developing immune and neural elements to create neurodevelopmental disturbances are poorly understood. We describe a model for investigating disorders of central nervous system development based on neonatal rat infection with Borna disease virus, a neurotropic noncytolytic RNA virus. Infection results in abnormal righting reflexes, hyperactivity, inhibition of open-field exploration, and stereotypic behaviors. Architecture is markedly disrupted in hippocampus and cerebellum, with reduction in granule and Purkinje cell numbers. Neurons are lost predominantly by apoptosis, as supported by increased mRNA levels for pro-apoptotic products (Fas, caspase-1), decreased mRNA levels for the anti-apoptotic bcl-x, and in situ labeling of fragmented DNA. Although inflammatory infiltrates are observed transiently in frontal cortex, glial activation (microgliosis > astrocytosis) is prominent throughout the brain and persists for several weeks in concert with increased levels of proinflammatory cytokine mRNAs (interleukins 1alpha, 1beta, and 6 and tumor necrosis factor alpha) and progressive hippocampal and cerebellar damage. The resemblance of these functional and neuropathologic abnormalities to human neurodevelopmental disorders suggests the utility of this model for defining cellular, biochemical, histologic, and functional outcomes of interactions of environmental influences with the developing central nervous system.

Connolly AM, Chez MG, Pestronk A, Arnold ST, Mehta S, Deuel RK: Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders. J Pediatr 1999 May;134(5):607-13.

Abstract:

Departments of Neurology and Pediatrics, Washington University , St. Louis Children's Hospital, St Louis, Missouri, USA .

OBJECTIVE: Etiologically unexplained disorders of language and social development have often been reported to improve in patients treated with immune-modulating regimens. Here we determined the frequency of autoantibodies to brain among such children. DESIGN: We collected sera from a cohort of children with (1) pure Landau-Kleffner syndrome (n = 2), (2) Landau-Kleffner syndrome variant (LKSV, n = 11), and (3) autistic spectrum disorder (ASD, n = 11). None had received immune-modulating treatment before the serum sample was obtained. Control sera (n = 71) were from 29 healthy children, 22 with non-neurologic illnesses (NNIs), and 20 children with other neurologic disorders (ONDs). We identified brain autoantibodies by immunostaining of human temporal cortex and antinuclear autoantibodies using commercially available kits. RESULTS: IgG anti-brain autoantibodies were present in 45% of sera from children with LKSV, 27% with ASD, and 10% with ONDs compared with 2% from healthy children and control children with NNIs. IgM autoantibodies were present in 36% of sera from children with ASD, 9% with LKSV, and 15% with ONDs compared with 0% of control sera. Labeling studies identified one antigenic target to be endothelial cells. Antinuclear antibodies with titers >/=1:80 were more common in children with ASD and control children with ONDs. CONCLUSION: Children with LKSV and ASD have a greater frequency of serum antibodies to brain endothelial cells and to nuclei than children with NNIs or healthy children. The presence of these antibodies raises the possibility that autoimmunity plays a role in the pathogenesis of language and social developmental abnormalities in a subset of children with these disorders.

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 Jun;14(6):388-94.

Abstract:

Johns Hopkins Hospital , Division of Pediatric Neurology, Baltimore, MD 21212, USA . acomimd@aol.com

Autism is an age-dependent neurologic disorder that is often associated with autoimmune disorders in the patients' relatives. To evaluate the frequency of autoimmune disorders, as well as various prenatal and postnatal events in autism, we surveyed the families of 61 autistic patients and 46 healthy controls using questionnaires. The mean number of autoimmune disorders was greater in families with autism; 46% had two or more members with autoimmune disorders. As the number of family members with autoimmune disorders increased from one to three, the risk of autism was greater, with an odds ratio that increased from 1.9 to 5.5, respectively. In mothers and first-degree relatives of autistic children, there were more autoimmune disorders (16% and 21%) as compared to controls (2% and 4%), with odds ratios of 8.8 and 6.0, respectively. The most common autoimmune disorders in both groups were type 1 diabetes, adult rheumatoid arthritis, hypothyroidism, and systemic lupus erythematosus. Forty-six percent of the autism group reported having relatives with rheumatoid diseases, as compared to 26% of the controls. Prenatal maternal urinary tract, upper respiratory, and vaginal infections; asphyxia; prematurity, and seizures were more common in the autistic group, although the differences were not

significant. Thirty-nine percent of the controls, but only 11% of the autistic, group, reported allergies. An increased number of autoimmune disorders suggests that in some families with autism, immune dysfunction could interact with various environmental factors to play a role in autism pathogenesis.

Singh V, Lin S, Yang V. Serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism. Clinical Immunology and Immunopathology 1998;89;105-108.
College of Pharmacy, University of Michigan, Ann Arbor, Michigan, 48109-1065, USA.

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. This study is the first to report an association between virus serology and brain autoantibody in autism; it supports the hypothesis that a virus-induced autoimmune response may play a causal role in autism. Copyright 1998 Academic Press.

Van Gent T, Heijnen CJ, Treffers PD: Autism and the immune system. J Child Psychol Psychiatry 1997 Mar;38(3):337-49.

Abstract:

University of Leijden , The Netherlands .

As our knowledge of the interactions of the immune, nervous and endocrine systems progresses, complex links with the origin and course of psychopathology in childhood are revealed. In this article the neuroimmunological literature on autism is reviewed. Relevant aspects of immune functioning and the neuroendocrine-immune network are described. We present the immunological findings in autistic patients within two related conceptual frameworks: a viral and an autoimmune hypothesis. Interpretation of data is hampered by conceptual and methodological differences between studies. Both the clinical significance of the immune changes and the causal connection between immune changes and psychopathological phenomena in autism remain to be elucidated. Recommendations for further research are given.

Warren RP, Singh VK, Averett RE, Odell JD, Maciulis A, Burger RA, Daniels WW, Warren WL: Immunogenetic studies in autism and related disorders. Mol Chem Neuropathol 1996 May-Aug;28(1-3):77-81.

Abstract:

Utah State University , Logan 84322, USA .

The major histocompatibility complex comprises a number of genes that control the function and regulation of the immune system. One of these genes, the C4B gene, encodes a product that is involved in eliminating pathogens such as viruses and bacteria from the body. We previously reported that a deficient form of the C4B gene, termed the C4B null allele (no C4B protein produced) had an increased frequently in autism. In this study we attempted to confirm the increased incidence of the C4B null allele in autism and investigated the presence of a C4B null allele in two other childhood disorders, attention-deficit hyperactivity disorder and dyslexia (reading disability). In addition, we explored the relationship of autism to the DR beta 1 gene, a gene located close to the C4B in autism. We confirmed the finding of an increased frequency of the C4B null allele in autism and found that the related disorders also had an increased frequency of this null allele. In addition, two alleles of the DR beta 1 gene also had significantly increased representation in the autistic subjects.

Warren RP, Singh VK: Elevated serotonin levels in autism: association with the major histocompatibility complex. Neuropsychobiology 1996;34(2):72-5.

Abstract:

Center for Persons with Disabilities, Utah State University , Logan 84322, USA .

Two of the most consistently observed biological findings in autism are increased serotonin levels in the blood and immunological abnormalities (including autoreactivity with tissues of the central nervous system). The purpose of this investigation was to determine if any relationship exists between these two sets of observations. Our laboratory has found and confirmed associations of the major histocompatibility complex (MHC) with autism. Since the MHC is known to regulate the immune system and is also associated with autoimmune disorders, we studied serum serotonin levels in 20 autistic subjects with or without MHC types previously found to be associated with autism. A positive relationship was observed between elevated serotonin levels and the MHC types previously associated with autism.

Singh VK: Plasma increase of interleukin-12 and interferon-gamma. Pathological significance in autism. J Neuroimmunol 1996 May;66(1-2):143-5.

Abstract:

Department of Psychiatry, University of Michigan, School of Medicine, Ann Arbor 48109-0656, USA.

Immune factors such as autoimmunity have been implicated in the genesis of autism, a neurodevelopmental disorder. Since autoimmune response involves immune activation, the plasma levels of interferon-alpha (IFN-alpha), interferon-gamma (IFN-gamma), interleukin-12 (IL-12), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and soluble intercellular adhesion molecule-1 (sICAM-1) were measured in autistic patients and age-matched normal controls. The levels of IL-12 and IFN-gamma were significantly (P < or = 0.05) higher in patients as compared to controls. However, IFN-alpha, IL-6, TNF-alpha, and sICAM-1 levels did not significantly differ between the two groups. Because macrophage-derived IL-12 is known to selectively induce IFN-gamma in T helper type-1 (Th-1) cells, it is suggested that IL-12 and IFN-gamma increases may indicate antigenic stimulation of Th-1 cells pathogenetically linked to autoimmunity in autism.

Scifo R, Cioni M, Nicolosi A, Batticane N, Tirolo C, Testa N, Quattropani MC, Morale MC, Gallo F, Marchetti B: Opioid-immune interactions in autism: behavioural and immunological assessment during a double-blind treatment with naltrexone. Ann Ist Super Sanita 1996;32(3):351-9.

Abstract:

Servizio di Psichiatria, Istituto OASI per lo Studio del Ritardo Mentale e l'Involuzione Cerebrale, Troina (Enna), Italy .

The emerging concept of opioid peptides as a new class of chemical messengers of the neuroimmune axis and the presence of a number of immunological abnormalities in infantile autism prompted us to correlate biological (hormonal and immunological) determinations and behavioural performances during treatment with the potent opiate antagonist, naltrexone (NAL). Twelve autistic patients ranging from 7 to 15 years, diagnosed according to DSM-III-R, entered a double-blind crossover study with NAL at the doses of 0.5, 1.0 and 1.5 mg/kg every 48 hours. The behavioural evaluation was conducted using the specific BSE and CARS rating scales NAL treatment produced a significant reduction of the autistic symptomatology in seven ("responders") out of 12 children. The behavioural improvement was accompanied by alterations in the distribution of the major lymphocyte subsets, with a significant increase of the T-helper-inducers (CD4+CD8-) and a significant reduction of the T-cytotoxic-suppressor (CD4-CD8+) resulting in a normalization of the CD4/CD8 ratio. Changes in natural killer cells and activity were inversely related to plasma beta-endorphin levels. It is suggested that the mechanisms underlying opioid-immune interactions are altered in this population of autistic children and that an immunological screening may have prognostic value for the pharmacological therapy with opiate antagonists.

Gupta S, Aggarwal S, Heads C: Dysregulated immune system in children with autism: beneficial effects of intravenous immune globulin on autistic characteristics. J Autism Dev Disord 1996 Aug;26(4):439-52. [No abstract available]

Warren RP, Yonk J, Burger RW, Odell D, Warren WL: DR-positive T cells in autism: association with decreased plasma levels of the complement C4B protein. Neuropsychobiology 1995;31(2):53-7.

Abstract:

Center for Persons with Disabilities, Utah State University , Logan 84322 , USA .

Autism is a developmental disorder characterized by severe communication, social and behavioral abnormalities. Over the past several years a fair amount of evidence has accumulated suggesting that some cases of autism may be associated with immune abnormalities and with products of the HLA complex including the C4B gene located in the class III region of HLA. This study sought additional evidence for an association of autoimmune processes with autism by investigating the presence of activated T cells in 26 autistic subjects. Fourteen of the autistic subjects had DR+ T cells, an indicator of activated T cells, but none of the autistic subjects had T cells expressing the interleukin-2 receptor, another indicator of T cell activation. Similar findings of incomplete or partial T cell activation have been reported in autoimmune disorders and in a recent study of autism. In the current investigation, the DR+ T cells were not found to be associated with age of the autistic patients but were inversely correlated with a decreased plasma level of the C4B protein. In conclusion, this study provides additional evidence for the involvement of an autoimmune mechanism in autism.

Daniels WW, Warren RP, Odell JD, Maciulis A, Burger RA, Warren WL, Torres AR: Increased frequency of the extended or ancestral haplotype B44-SC30-DR4 in autism. Neuropsychobiology 1995;32(3):120-3.

Abstract:

Center for Persons with Disabilities, Utah State University , Logan 84322, USA .

Autism likely results from several different etiologies or a combination of pathological mechanisms. Recent studies suggest that this disorder may be associated with immune abnormalities, pathogen-autoimmune processes and perhaps the major histocompatibility complex (MHC). In a preliminary study we found that 22 autistic subjects had an increased frequency of the extended or ancestral MHC haplotype B44-SC30-DR4. The current study attempted to confirm this observation by studying 23 additional randomly chosen autistic subjects, most of their parents and 64 unrelated normal subjects. In agreement with earlier findings B44-SC30-DR4 was associated with autism. In combining the data from the original and current studies, B44-SC30-DR4 or a substantial fragment of this extended haplotype was represented in 40% of the autistic subjects and/or their mothers as compared to about 2% of the unrelated subjects. It is concluded that one or more genes of the MHC is (are) involved in the development of some cases of autism.

Singh V. K., Warren R. P., Odell J. D. Warren W. L., Cole P.: Antibodies to Myelin Basic Protein in Children with Autistic Behavior. Brain, Behavior, and Immunity 7, 97 - 103, 1993.

Abstract: Biomedical Division, Center for Persons with Disabilities, Logan, Utah .

Based on a possible pathological relationship of autoimmunity to autism, antibodies reactive with myelin basic protein (anti-MBP) were investigated in the sera of autistic children. Using a screening serum dilution of 1:400 in the protein-immunoblotting technique, approximately 58% (19 of 33) sera of autistic children (< or = 10 years of age) were found to be positive for anti-MBP. This result in autistics was significantly (p < or = .0001) different from the controls (8 of 88 or only 9% positive), which included age-matched children with normal health, idiopathic mental retardation (MR) and Down syndrome (DS), and normal adults of 20 to 40 years of age. Since autism is a syndrome of unknown etiology, it is possible that anti-MBP antibodies are associated with the development of autistic behavior.

Singh V.K., Warren R.P Odell J.D., and Cole P.: Changes of soluble interleukin-2, interleukin-2 receptor, T8 antigen, and interleukin-1 in the serum of autistic children. Immunology and Immunopathology 61, 448-455, 1991.

Abstract:

Neuroimmunology Laboratory, Utah State University, Logan 84322-6800.

Immune abnormalities in autistic children led us to study for indirect evidence of immune activation as measured by the serum analysis of soluble interleukin-2 (sIL-2), interleukin-2 receptor (sIL-2R), T8 antigen (sT8), and interleukin-1 (sIL-1). The serum concentration of these soluble antigens was quantitated by enzyme-linked immunosorbent assays. The concentration of sIL-2 and sT8, but not of sIL-2R and sIL-1, antigens was significantly (P less than 0.05) increased in the sera of autistic children over that in the control healthy children or children with mental retardation (non-Down's syndrome). This finding indirectly indicates that the activation of a subpopulation of T cells occurs in some children with autism.

Yonk, L.J., Warren , R.P., Burger, R.A., Cole, P., Odell, J.D., Warren , W.L., White, E., and Singh, V.K.: CD4+ helper T cell depression in autism. Immunol. Lett. 25, 341 - 346, 1990.

Abstract:

Developmental Center for Handicapped Persons, Utah State University , Logan 84322-6800.

CD4+ (helper) T cells are a heterogenous population of lymphocytes including at least two distinct subpopulations. To investigate the possibility that immune abnormalities in some subjects with autism may involve abnormal distributions of CD4+ and/or CD8+ cells, (suppressor) T cells, peripheral blood lymphocytes of 25 autistic subjects were characterized with monoclonal antibodies and flow cytometry. The autistic subjects had a significantly lower percentage and number of CD4+ cells, a lower number of T cells (CD2+ cells) and B cells (CD20+ cells), and a lower percentage and number of total lymphocytes than siblings and normal subjects. The level of blood values for female subjects appeared lower than those for males as compared to normal subjects of the same sex. These results suggest that a decrease in CD4+ cells is associated with autism.

Warren, R. P.,Yonk, L. J., Burger, R. A., Cole, P., Odell, J.D., Warren, W.L., White, E., and Singh, V.K.: Deficiency of suppressor-inducer (CD4+CD45RA+) T cells in autism. Immunol. Invest. 19, 245-251, 1990.

Abstract:

Developmental Center for Handicapped Persons, Utah State University , Logan 84322.

CD4+ cells are a heterogenous population of lymphocytes including at least two distinct subpopulations: CD45RA+ cells, inducers of suppressor T cells and CDw29+ cells, inducers of helper function for antibody production. To investigate the possibility that immune abnormalities in autism may involve abnormal distribution of these helper subpopulations, monoclonal antibodies were used in flow cytometric analysis to characterize peripheral blood lymphocytes of 36 subjects with autism. The autistic subjects as compared to a group of 35 healthy age-matched subjects had a significantly reduced number of lymphocytes, a decreased number of CD2+ T cells and reduced numbers of CD4+ and CD4+CD45RA+ lymphocytes. The numbers of B (CD20+) cells, suppressor T (CD8+) cells, inducers of helper function (CD4+CDw29+) and natural killer (CD56+) cells were not altered in the autistic subjects. Our results suggest that an alteration in the suppressor-inducer T-cell subset is associated with autism.

Warren R. P., Cole P., Odell J. D., Pingree C., Warren L., White E., Yonk J., Singh V. K.: Detection of Maternal Antibodies in Infantile Autism. J. Am. Acad. Child Adolesc. Psychiatry, 29:6, November 1990.

Abstract:

Developmental Center for Handicapped Persons, Utah State University , Logan 84322.

Maternal antibodies reactive with antigenic proteins expressed on the cell surface of paternal lymphocytes can be detected in couples with histories of more than one miscarriage or stillbirth. It is possible, but not proven, that these antibodies also react with tissues of the fetus and result in fetal death. Since many mothers of autistic children have a history of pregnancy disorder, antibodies were studied in 11 mothers of autistic children who were 6 years of age or younger. Six of the mothers had antibodies that reacted with lymphocytes of the autistic child. Five of these six mothers had a history of pregnancy disorder. Since antigens expressed on lymphocytes are found on cells of the central nervous system and, perhaps, other tissues of the developing embryo, it is suggested that aberrant maternal immunity may be associated with the development of some cases of infantile autism.

Root-Bernstein RS, Westall FC: Serotonin binding sites. II. Muramyl dipeptide binds to serotonin binding sites on myelin basic protein, LHRH, and MSH-ACTH 4-10. Brain Res Bull 1990 Dec;25(6):827-41.

Abstract:

Department of Physiology, Michigan State University , East Lansing 48824.

Previously, we reported the existence of structurally similar serotonin binding sites on myelin basic protein, LHRH, and MSH-ACTH 4-10. We now report that the adjuvant peptide, muramyl dipeptide (N-acetyl-muramyl-L-Ala-D-isoGln) also binds to these sites. This observation may help to explain previous observations of serotonin-like activity by muramyl peptides, including the promotion of slow-wave sleep and fever induction. The observation may also provide an important link between the immune system and the nervous system that may explain the role of muramyl dipeptide adjuvants in causing autoimmune diseases to serotonin-regulated proteins and their receptors, as well as the alterations in serotonin levels that are often observed in autoimmune diseases. The observation provides concrete evidence for a dual-antigen hypothesis for the induction of autoimmune diseases by an adjuvant-peptide complex. Application of such a mechanism for induction of autoimmunity may be of importance in understanding a number of postinfectious and postvaccinal neuropathies, and suggests a possible etiology for autism, in which many patients have high blood serotonin levels, autoimmune reactions to myelin basic protein, and antibodies to serotonin binding sites. Finally, the observation suggests that glycopeptides may act as neurotransmitters.

Singh, V.K, Fudenberg, H. H., Emerson, D. and Coleman, M. : Immunodiagnosis and immunotherapy in autistic children. Ann. N. Y. Acad. Sci. 540, 602-604, 1988. [No abstract available]

Meulen Ter Volker: Autoimmune Reactions Against Myelin Basic Protein Induced by Corona and Measles Viruses. Annals of The New York Academy of Sciences, Advances in Neuroimmunology, Vol. 540, 1988. [No abstract available]

Ferrari P, Marescot MR, Moulias R, Bursztejn C, Deville Chabrolle A, Thiollet M, Lesourd B, Braconnier A, Dreux C, Zarifian E, et al: Immune status in infantile autism. Correlation between the immune status, autistic symptoms and levels of serotonin [Article in French]. Encephale 1988 Sep-Oct;14(5):339-44.

Abstract:

Service de Psychotherapie, l'Enfant et de l'Adolescent, Hopital Robert Debre, Reims.

In sixteen autistic children high values of IgG and a high level of lymphocyte stimulation with PHA were observed. Principal component analysis showed: 1) a significant correlation between basic lymphocyte mitogenic activity and the clinical symptoms opposition and hyperactivity, 2) a significant correlation between high Ig levels, high PHA stimulation responses and the main autistic symptoms (withdrawal, inaffectivity, hypoactivity, mannerism, stereotypy and negatively echolalia), 3) a significant correlation with serotonin uptake by platelets and high immunological responses. Such correlations are strongly in favor of an immunologic component in autistic disease.

Warren RP, Foster A, Margaretten NC: Reduced natural killer cell activity in autism. J Am Acad Child Adolesc Psychiatry 1987 May;26(3):333-5. [No abstract available]

Warren RP, Margaretten NC , Pace NC, Foster A: Immune abnormalities in patients with autism. J Autism Dev Disord 1986 Jun;16(2):189-97.

Abstract:

We have begun an investigation on the immune systems of patients with autism in attempt to determine if immune mechanisms are involved in the development of this severe developmental disorder. A study of 31 autistic patients has revealed several immune-system abnormalities, including reduced responsiveness in the lymphocyte blastogenesis assay to phytohemagglutinin, concanavalin A, and pokeweed mitogen; decreased numbers of T lymphocytes; and an altered ratio of helper to suppressor T cells. Immune-system abnormalities may be directly related to underlying biologic processes of autism, or these changes may be an indirect reflection of the actual pathologic mechanism.

Todd RD: Pervasive developmental disorders and immunological tolerance. Psychiatr Dev 1986 Summer;4(2):147-65.

Abstract:

A wide range of studies in man and other species suggest that early compromise of immunological tolerance (both maternal-fetal and self) may lead to severe and varied cognitive deficits. This article briefly reviews what is known of the genesis and maintenance of normal tolerance and current ideas on pathological deviances in tolerance. These ideas are discussed in relation to risk

factor, family, twin, biochemical, anatomical, and immunological studies of pervasive developmental disorders (particularly infantile autism). A range of immunological injury hypotheses for the genesis of the pervasive developmental disorders are considered and technical problems in deciding among them are presented.

Weizman, A., Weizman, R., Szekely, G.A., Wijsenbeek, H., and Livni, E: Abnormal immune response to brain tissue antigen in the syndrome of autism. Am. J. Psychiatry 7, 1462-1465, 1982.

Abstract:

Cell-mediated immune response to human myelin basic protein was studied by the macrophage migration inhibition factor test in 17 autistic patients and a control group of 11 patients suffering from other mental diseases included in the differential diagnosis of the syndrome of autism. Of the 17 autistic patients, 13 demonstrated inhibition of macrophage migration, whereas none of the nonautistic patients showed such a response. The results indicate the existence of a cell-mediated immune response to brain tissue in the syndrome of autism.

Stubbs EG, Crawford ML: Depressed lymphocyte responsiveness in autistic children. J Autism Child Schizophr 1977 Mar;7(1):49-55.

Abstract:

Although there are associations linking autism with prenatal rubella, cytomegalovirus, syphilis, and varicella, the etiology of the autistic state remains obscure. Host defense against the etiologic agents postulated to be responsible for the autism-associated syndromes is believed to be primarily of the cell-mediated type. In this preliminary study, cellular immune function was assessed in vitro by phytohemagglutinin (PHA) stimulation of lymphocyte cultures. Twelve autistic children and 13 control subjects were compared. The autistic group exhibited a depressed lymphocyte transformation response to PHA when compared to the control subjects (p less than .01).

Stubbs EG: Autistic children exhibit undetectable hemagglutination-inhibition antibody titers despite previous rubella vaccination. J Autism Child Schizophr 1976 Sep;6(3):269-74.

Abstract:

The etiology of autism is unknown, but autism has been associated with a number of diseases, including prenatal rubella. Rubella vaccine challenge was used in an attempt to retrospectively diagnose prenatal rubella in autistic children. This test was selected because unresponsiveness of antibody titer has been reported as helpful in retrospective diagnosing of prenatal rubella. Fifteen autistic children and 8 controls matched for age were challenged with rubella vaccine. Rubella vaccine challenge did not differentiate autistic children from the control subjects. However, 5 of 13 autistic children had undetectable titers despite previous vaccine; all control subjects had detectable titers. This finding of undetectable titers in autistic children suggests these children may have an altered immune response.

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