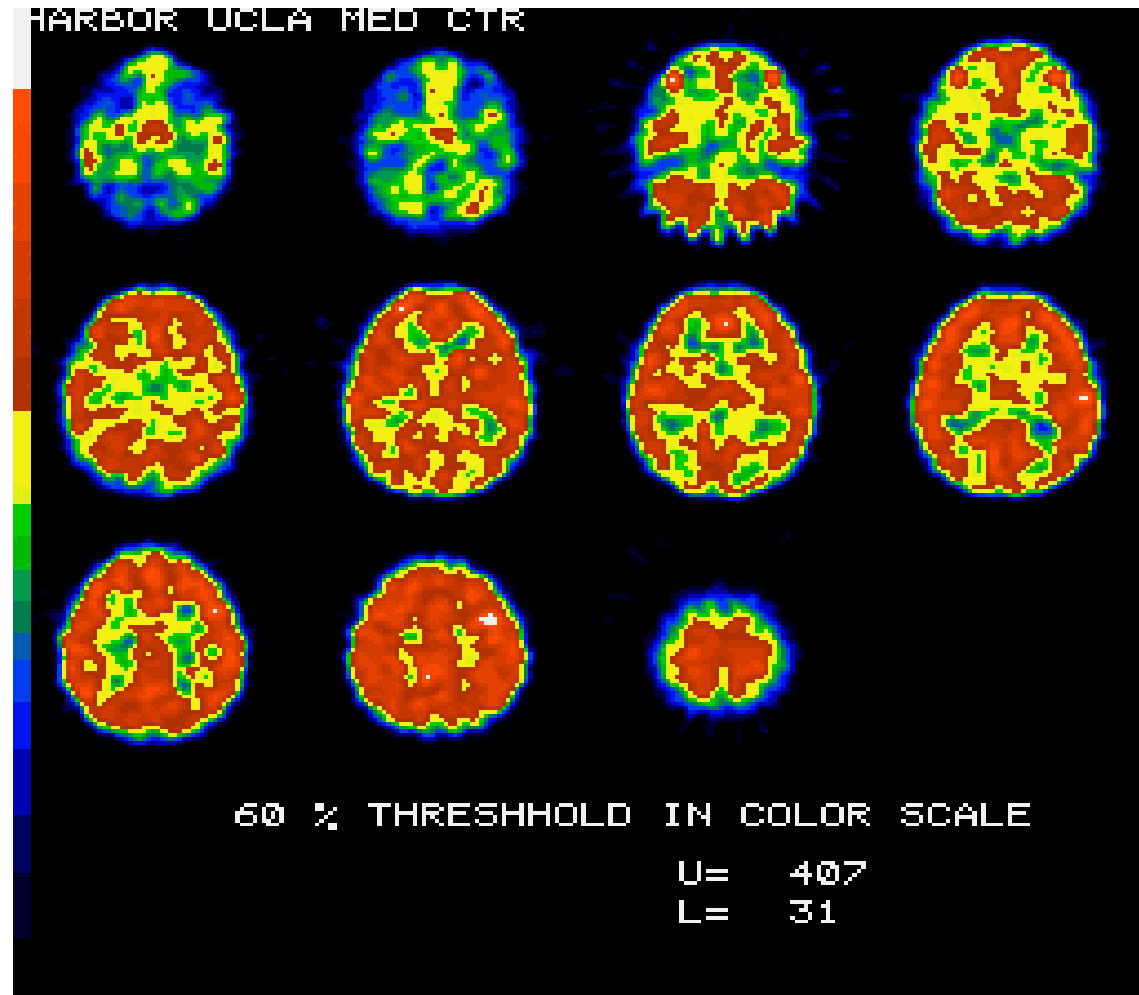


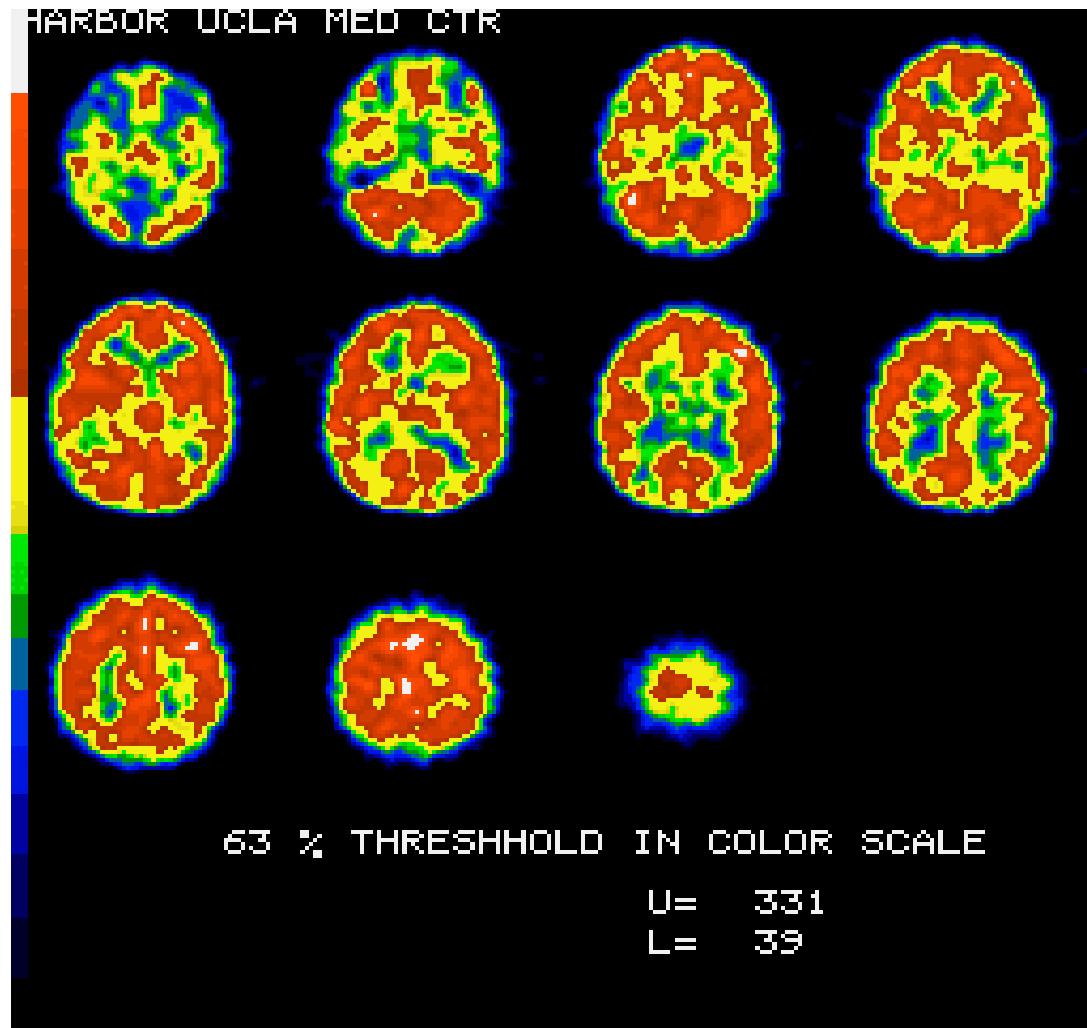
NeuroSPECT

- 5 y/o M - "Autistic Syndrome"



NeuroSPECT

- 8 y/o F - "Autistic Syndrome"





CONCLUSIONS - Implications:

- **Temporal lobe hypoperfusion and other areas of dysfunction remains in spite of multiple various therapies used by these children.**
- **We are looking at anatomical markings, defining Autism / PDD dysfunction, correlating to models proposed by behavioral neurologists**
- ***Increased frontal perfusion* may be related to “hyperfrontality” disorder, and *cerebellar hypoperfusion* to motility / motor impairment.**

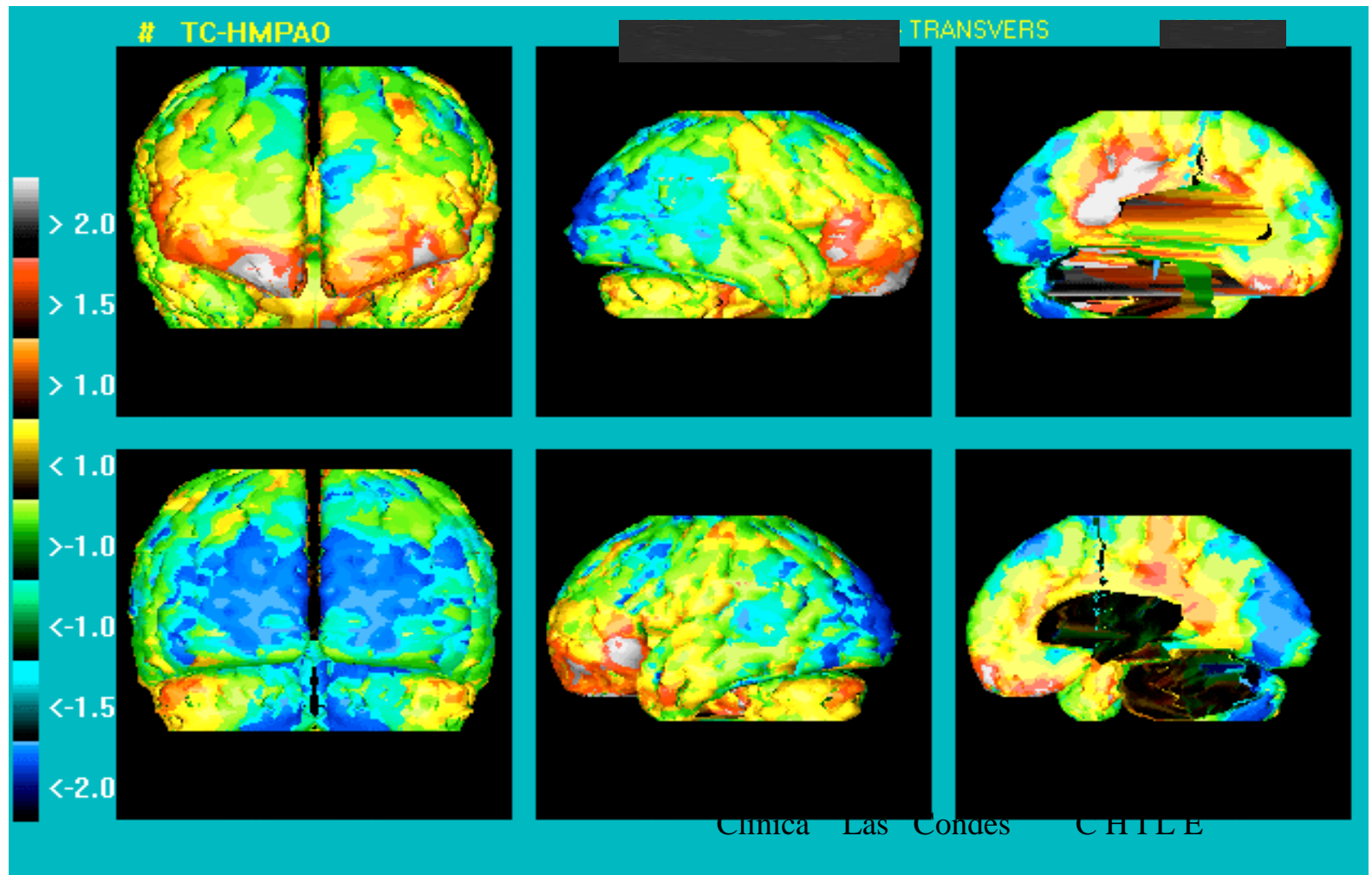


CONCLUSIONS - Implications:

(cont.)

- Autism, Pervasive Development Disorder (PDD), Attention Deficit Hyperactive Disorder (ADHD), and Obsessive and Compulsive Disorder (OCD) involve **significant frontal and temporal lobe dysfunction**
 - As noted, we have been using NeuroSPECT to image cerebral abnormalities of perfusion/function in Autism, ADHD, OCD, and other neuro-cognitive disorders for **many years now**

Autism:



FRONTAL AND TEMPORAL LOBE DYSFUNCTION IN AUTISM AND OTHER RELATED DISORDERS: ADHD AND OCD



Autism, 4 years old girl. Demonstrates hypoperfusion in areas 9 and 10 in the frontal lobes, while there is increased perfusion in areas 8 and upper 9. Area 38 in temporal lobes is hypoperfused and also both occipital lobes. Importantly in this case there is bilateral increase of function in both anterior cingulate gyri, area 24 of Brodmann (this is related to ADD)

Functional Deficits in Autistic Disorder: Characterization by Technetium-99m-hmpao and

SPECT J.M.Mountz, C. Tolbert, Duncan W. Lill, et. al.

The Journal of Nuclear Medicine. Vol.36. NO 7 July 1995

Results: In the autistic patients –

Abnormally low rCBF values located predominately in the **temporal and parietal lobes**, with the **left** cerebral hemisphere showing **greater** rCBF abnormalities than the **right**.

No difference in rCBF values were found between the two normal and the five other controls

Abnormal temporal lobe function possibly plays a role in the pathogenesis of autism, since normal functioning of the amygdala and hippocampus is crucial to the regulation and integration of affect, memory and learning

Temporal Lobe Dysfunction in Childhood Autism: A PET Study

Zilbovicius M, Boddaert N, Belin P, Poline JB, Remy P, Mangin JF, Thivard L, Barthelemy C, Samson Y *Am J Psychiatry* 2000 Dec 1;157(12):1988-1993

- **OBJECTIVE:** The nature of the underlying brain dysfunction of childhood autism, a life-long severe developmental disorder, is not well understood
- **METHOD:** To test this hypothesis, regional cerebral blood flow was measured with positron emission tomography (PET) in 21 children with primary autism and in 10 nonautistic children with idiopathic mental retardation.
- **RESULTS:** The first autistic group had a **highly significant hypoperfusion in both temporal lobes centered in associative auditory and adjacent multimodal cortex**, which was detected in 76% of autistic children. Virtually identical results were found in the second autistic group in the extension study
- **CONCLUSIONS:** PET and voxel-based image analysis revealed a localized dysfunction of the temporal lobes in school-aged children with idiopathic autism.

WHAT MAKES THIS “DIFFERENT?”



Medical Support - Objective Findings

The last **20+ years of medical** research

- **New** diseases / dysfunction
- **New** understanding of the “Neuro-Immune” axis
- Multiple changes / **increase “auto-immune” disease**
- Multiple changes / **increase in cognitive dysfunction**
- Medical, scientific, and “lay” press **support . . .**
 - **Significant increase in environmental / immune diseases in mammals**
 - **“Children are mammals!”**



THE IMMUNE CONNECTION

This physician's opinion:

- **“True” patho-physiology - cytokines / combination of cytokines / chemokines affected by:**
 - **Other influences** or combination of **factors** effecting the **immune system**
 - **Increasing probability of viral / retro-viral role**
 - ***Genetically susceptible individual***



**MANY CHILDREN & ADULTS
WITH AUTISM/PDD, ADD/ADHD,
CFS/CFIDS - N.I.D.S.**

ALLERGIES OR INTOLERANCES

Family history:

Eczema

Migraines (especially in mothers)

Hay fever

Asthma

Other **"Auto-Immune" disease**

(i.e. Thyroiditis, Lupus,
Rheumatoid, etc.)



Common Linkage / Connection - NIDS

- Neuro Immune Dysfunction Syndromes
 - A Medical Way to look with new understanding, new technologies, new therapy potentials for:
 - Autism / PDD
 - ADHD
 - OCD, Tourette's
 - CFS / CFIDS
 - ?? "other" neuro-immune mediated disorders / CNS dysfunctions

NIDS

(Neuro Immune Dysfunction Syndromes)

- For whatever the reasons (genetic, environmental, a combination of viruses, vaccines, immune system “insults,” etc.), what is occurring appears to be an *immune mediated, abnormal "shut down" of blood flow in the brain and therefore central nervous system function.*

NeuroSPECT Findings in Children with Chronic Fatigue Syndrome

NEUROSPECT: ASSESSMENT OF ABNORMAL DISTRIBUTION OF RCBF IN CFIDS VS. "AUTISTIC SYNDROME CHILDREN."

NeuroSPECT Findings in Children with Chronic Fatigue Syndrome

Michael J. Goldberg, MD
Ismael Mena, MD
Jacques Darcourt, MD

ABSTRACT. Background. NeuroSPECT studies have described specific abnormalities in cerebral perfusion in adults with criteria for Chronic Fatigue Syndrome. This reports findings in 13 children with criteria for Chronic Fatigue Syndrome.

Objective. NeuroSPECT findings in 13 CFS/CFIDS children.

Methods. Thirteen children meeting CDC criteria for CFS/CFIDS, were evaluated using NeuroSPECT imaging utilizing Xenon 133 and Tc-99m-HMPAO (1).

Results. In 13 children, hypoperfusion was observed at 42 ± 10 ml/min/100g, $p < 0.0001$ in the left temporal lobe and at 45 ± 11 , $p < .001$ in right temporal lobe. Statistically significant hypoperfusion was also observed in both parietal lobes and at 50 and 53 ml/min/100g, $p < 0.05$ in the frontal lobe of the right hemisphere. Quantitated HMPAO demonstrated bilateral orbitofrontal and anterior temporal hypoperfusion. There was also hypoperfusion in the dorsal aspects of both frontal lobes and both parietooccipital lobes.

Conclusion. NeuroSPECT is presented as a quantifiable, reproducible tool that can allow us to document a cohort of children defined as CFS/CFIDS. [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: getinfo@haworth.com]

KEYWORDS. CFS, CFIDS, spect scan, pediatrics, children, cerebral blood flow, neurospect

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Journal of Chronic Fatigue Syndrome, Vol. 3(1) 1997
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PEDIATRICS & YOUNG ADULTS
ADHD/ADD - LEARNING DISABILITIES
IMMUNE DYSFUNCTION
AUTISM

NEUROSPECT: ASSESSMENT OF ABNORMAL DISTRIBUTION OF RCBF IN CFIDS VS. "AUTISTIC SYNDROME CHILDREN."

Michael Goldberg, Ismael Mena, Bruce Miller, and Carmen Thomas.
Dept. of Nuclear Medicine, Imaging Center, Harbor UCLA Medical Center, Torrance, Ca.

OBJECTIVE: To compare NeuroSpect finding in 25 children diagnosed "Autistic Syndrome / PDD" with 13 children with CFS / CFIDS vs. normals.

METHODS: We report on quantitative (Xe133) rCBF and high resolution HMPAO SPECT in 25 children meeting criteria of DSM IV for autism, compared with 13 children meeting CDC criteria for chronic fatigue syndrome (CFIDS) and 13 normal children (HMPAO). Ages were 5.5 ± 2.5 years, 13 ± 3 years and 9.3 ± 3.2 years respectively. Male/female ratios were 22/3, 7/6 and 8/5 respectively. RCBF was imaged with a brain dedicated imaging device (Shimatzu, Headtome) after inhalation of 1,110 MBq of Xe133 gas, and with a high resolution fan beam collimator after IV injection of 370 - 740 MBq of Tc99m HMPAO. ROIs were determined manually for Xe133 and automatically set for HMPAO (64 transaxial cut, in 6 adjacent 1 cm cuts above basal ganglia).

RESULTS:

	Xe133 rCBF (ml/min/100g)		
	Max. Flow	Min. Flow	Avg. Flow
1. Autism	116±28 **	49±10 * 92±22 ***	vs2
2. CFIDS	86±11	35±5	63±7 **vs3
3. Normals			62±9x

$p < 0.001$ ***
0.002 **
0.02 *

x Chiron et al., J.Nuc. Med; 1992:33,696-703

In the Autistic children, maximal rCBF was observed in frontal lobes, while minimal rCBF was detected in temporal and occipital lobes and cerebellum. HMPAO uptake was 0.50 ± 5 in occipital lobes and in frontal lobes 0.82 ± 4 , $p < 0.0001$, while in Normals it was 0.78 ± 5 , without significant gradient. In the CFIDS children, hypoperfusion is observed at 42 ± 10 ml/min/100g, $p < 0.0001$ in the left temporal lobe and at 45 ± 11 , $p < .001$ in right temporal lobe. There is furthermore hypoperfusion with similar statistical significance in both parietal lobes and at 50 and 53 ml/min/100g, $p < 0.05$ in the frontal lobe of the right hemisphere.

SUMMARY: Brain Spect Scan results are presented along with some clinical observations of these particular groups of patients. This tool may open the door to a more physiologic/medical approach to this process in children. Comparisons are made with the finding in children with CFIDS and those "labeled" Autistic Syndrome / PDD. The observation of temporal hypoperfusion in adults and children with CFS/CFIDS, may help define Autism as a disorder of impaired relations with the surrounding environment determined by the temporal hypofunction leading as a consequence to a diaschetic hypofunction of visual cortex and cerebellum. The mechanisms for this abnormality need to be investigated using activation techniques and other approaches i.e.: evaluation of possible immune dysregulation, etc.

NIDS

(Neuro –Immune Dysfunction Syndromes)

(cont.)

- In **adolescents and adults**, this dysfunction may manifest itself as **CFIDS** (Chronic Fatigue Immune Dysfunction Syndrome), **ADHD “variants”**, and various **other atypical auto-immune disorders** associated with neuro-immune dysfunction
- In **older children**, it is seen as **variants of ADD (Attention Deficit Disorder) / ADHD**
- And in **younger children/infants**, it appears as **“Autism, Autistic syndrome, PDD, etc.”**

NIDS –

Family “Connections”

- Mother or Father with **CFS** or “**other**” immune mediated disorder
- Older child (or two) with **ADHD** (or other learning disorder **LD**)
- Younger child (or two) with **Autism / PDD**

CHARACTERISTICS:

Autism vs. CFIDS

Disturbances in the rate of appearance of physical, social, and language skills.

- Abnormal responses to sensations.
- A combination of sight, hearing, touch, pain, balance, smell, taste, and the way a child holds his body are affected.
- Speech and language are absent or delayed - thinking capabilities may be present.
- Abnormal WAYS of relating to people, objects, and events

- Distressing memory and concentration loss, word blocking, forgetful, “foggy”
- Overwhelmed by loud / conflicting noises, etc.
- Impaired judgment
 - Inability to link up auditory and visual input
- Dyslexic-like symptoms
- Difficulty maintaining attention
- Difficulties/impairment in inputting, encoding and retrieving information
 - Difficulties comprehending and recalling what has been read

NIDS

(Neuro –Immune Dysfunction Syndromes)

(cont.)

- The multiple secondary metabolic, physiologic, and immune markers that are abnormal in these children, "make sense" when you think of the bigger picture and consider the primary cause of autism as neuro-immune dysfunction, creating multiple cellular / mitochondrial dysfunctions



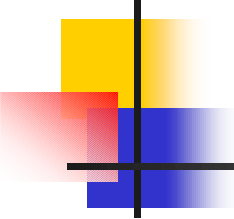
Immune / Viral Patterns on Clinical Blood Work Showing:

- **Low NK cells**
 - **< 6% = 59 / 145 (41%)**
- **Elevated and Low CD4 and / or CD8 cells**
- **Elevated Gliadin IgG's**
- **Positive ANA's**
- **Abnormally LOW Sed Rates (ESR)**
- **Multiple elevated viral titers**
 - EBV, HHV6, CMV
 - “multiple” other viral IgG elevations
- **Low Ferritins**
- **“Shifts to the right” on food screens**



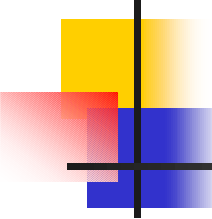
Pertinent Articles:

- **Biochemical dysregulation of the 2-5A I Rnase L antiviral defense pathway in Chronic Fatigue Syndrome**
 - Authors: Robert 1. Suhadolnik*, Daniel L Pecerson**, Paul R Cheney+, Susan E Horvath*, Nancy L Reichenbach*. Karen O'Brien**, Vincent Lombardi**, Suzanne Welsch++, Elizaoeth G. Furr+, Ramamurthy Charubala***, and Wolfgang Pfliederer**** Temple University School of Medicine, Philadelphia, PA - **IMMUNE ACTIVATION**
- **Increased activation of human herpesvirus-6 (HHV-6, but not human herpesvirus-7 (HHV-7) or human herpesvirus-8 (HHV-8), in Chronic Fatigue Syndrome (CFS) patients**
 - Authors: D.V. Ahlashi*+, S. Marsh*, M. Handy*, J. Whilman*, D. Viza**, O. Krueger*** and P.H. Leviine**** Advanced Biotechnologies Inc. Columbia, MD)+Georgetown University School of Medicine, Washington, DC - **PERSISTENT REACTIVATION**



Persistent Active Human Herpes virus Six (HHV-6) Infections in Patients With Chronic Fatigue Syndrome

- Authors: Konstance K Knox Ph.D.*; Joseph H. Brewer, M.D.** , and Donald R. Carrigan, Ph.d*. *Herpesvirus Diagnostics, Inc. and Institute for Viral Pathogenesis; 12346W. Layton Ave. Greenfield, Wisconsin 532281 and**Infectious Diseases; St. Luke's Hospital; Kansas City, Missouri.
- **Conclusion:** These studies demonstrate that a sizable proportion (30% to 70%) of patients with CFS suffer from an **active persistent infection with HHV-6.**
- Active HHV-6 infections may be especially prevalent in CFS patients with **CNS involvement**, consistent with the **highly neuroinvasive nature of HHV-6**



Invasion by Human Herpesvirus 6 and Human Herpesvirus 7 of the **Central Nervous System** in Patients With Neurological Signs and Symptoms

Yoshikawa T, Ihira M, Suzuki K, Suga S, Matsubara T, Furukawa S, Asano Y
Department of Pediatrics, Fujita Health University School of Medicine,
Aichi, Japan. tetsushi@med.nagoya-u.ac.jp
Arch Dis Child 2000 Aug;83(2):170-1

- Human herpesvirus 6 (**HHV-6**) and **HHV-7** DNA was detected in cerebrospinal fluid (CSF) and peripheral blood mononuclear cells
- The seven **HHV6** CSF viruses were all variant **B**
- **CONCLUSION:** These data suggest that **HHV-7** may invade the **CNS**

Human Herpesvirus-6 Associated Encephalitis With Subsequent Infantile Spasms and Cerebellar Astrocytoma

Rantala H, Mannonen L, Ahtiluoto S, Linnavuori K, Herva R, Vaeheri A, Koskiniemi M Department of Paediatrics, University of Oulu, Finland.
Heikki.Rantala@oulu.fi Dev Med Child Neurol 2000 Jun;42(6):418-21

- **14 month-old girl**
 - 3 days of fever, **floppiness**, and diffuse urticarial exanthem.
- **Developed encephalitis and carditis**
 - 1 week later > **intractable seizures**
- On **days 14 and 34** (after the onset of symptoms) a human **herpesvirus-6 (HHV-6) genome** in **cerebrospinal fluid** was identified by polymerase chain reaction (**PCR**)
- **Convulsions** > “**typical**” infantile spasms with hypsarrhythmic
- Gradually **lost her social contact and ability to walk and sit**

Epidemiology of Human Herpesvirus 6 (HHV-6) Infection in Pregnant and Non-pregnant Women

Baillargeon J, Piper J, Leach CT Departments of Pediatrics, The University of Texas Health Science Center at San

Antonio J Clin Virol 2000 May;16(3):149-57

- Little information available regarding HHV-6 infection in women of reproductive age
 - University Family Planning Clinic
- **RESULTS: All subjects were HHV-6 antibody positive**
 - **Geometric mean titers of HHV-6 antibodies were significantly higher among nonpregnant versus pregnant women.**
 - **Moreover, a higher proportion of nonpregnant versus pregnant women had antibody titers ≥ 160 and ≥ 320 .**
- **Low rates of HHV-6 shedding in the genital tract were observed for both groups**
- Further longitudinal studies are required to assess the consequences of **maternal HHV-6 infection.**



Encephalitis Caused by Human Herpesvirus-6 in Transplant Recipients: Relevance of a Novel Neurotropic Virus

Singh N, Paterson DL Veterans Affairs Medical Center and University of Pittsburgh, Thomas E Starzl Transplantation Center Transplantation 2000

Jun 27;69(12):2474-9

- **BACKGROUND: Human herpesvirus-6 (HHV-6) is a neurotropic virus**
 - **HHV-6 encephalitis** occurred a median of 45 days (range 10 days to 15 months) after transplantation
 - **Mental status changes**
 - **Confusion to coma**
 - **Seizures**
 - **Headache**
- **Focal neurologic findings** occurred in **only 17%** of the patients
- **Cerebrospinal fluid pleocytosis was generally lacking**
- **CONCLUSIONS: HHV-6 may be associated with encephalitis after transplantation** and warrants consideration in transplant recipients with encephalitis of unidentifiable etiology

Pituitary-adrenal and Autonomic Responses to Stress in Women After Sexual and Physical Abuse in Childhood

Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CB **JAMA** 2000 Aug 2;284(5):592-7 Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine

■ **CONTEXT:**

- Evidence suggests that **early adverse experiences** play a preeminent role in **development of mood and anxiety disorders** and that **corticotropin-releasing factor (CRF)** systems may mediate this association

■ **RESULTS:**

- Women with a **history of childhood abuse** exhibited **increased pituitary-adrenal and autonomic responses to stress** compared with controls
- Women with a **history of childhood abuse and a current major depression diagnosis** exhibited a more than **6-fold greater ACTH response to stress than age-matched controls**



Consultants comment:

A diagnosis of autistic disorder is based on a **particular developmental pattern in conjunction with current behaviors.**

- ⑩ There must be qualitative impairments in social interaction and communication, as well as restricted, repetitive, and stereotyped patterns of behaviors.
 - ⑩ Delays in social interaction, language as used in social communication, or symbolic or imaginative play must be evident before age three.

Past Medical History

"PMH = ILLNESS"

- Eczema or hives
- Frequent ear infections
- Enuresis
- Frequent urination
- Very fidgety
- Trouble concentrating
- Self stemming
- Eye contact variable



"PMH = ILLNESS"

(cont.)

- Disturbs others in class
- **Sensory processing** difficulty
- **Vestibular** dysfunction
- **Auditory processing** difficulties
- Behavioral issues
- Very affectionate
- Hyperactive
- Sleep difficulties
 - *Wakes tired in AM*



"PMH = ILLNESS"


(cont.)

-
- Tuned out
 - Impairment with non-verbal behaviors
 - Failure to develop peer relationships
 - Lack of sharing interests
 - Impairment to initiate or sustain speech
 - Lack of varied or spontaneous play
 - Inflexible adherence to rituals
 - Repetitive motor mannerisms
 - Fine motor abnormal



DISEASE (di-zez´):

- Recognized **etiologic agent(s)**
 - Associated with **Herpes** and other **viral** infections
- Identifiable group of **signs and symptoms**
 - “Autism” - DSMIV 299.00
 - “Potential **Immune** and other **Markers**”
- Consistent **anatomical alterations**
 - **NeuroSPECT!**



HUGE implications “This IS a **Disease**”

(**NOT** a developmental disorder, a congenitally “miswired” brain, etc.)

- **“Disease”** means these children were born with **normally functioning brains** that became dysfunctional
 - That means they **can be fixed**, in theory they can **work normally**, again
 - You **cannot** “fix” / recover from a **developmental disorder**, you **can** from a **disease**
- All of this has even more profound implications in light of the work from **leading institutions** **showing**:
 - The brain is more **pliable** than we thought (implying **late redevelopment is still possible**)
 - The **importance of early, correct laying down of pathways / tracts** – as the brain evolves and develops



Implications - Expectations

- **Past focus** for autistic children has been on **trainability, cooperation, behavior, NOT** on improving the **cognitive processing**
 - As a parent recently noted, *a child with “Autism” is **not suppose to be able to recover**, develop “functions” they are not suppose to have . . .rather **one tries to compensate and work with the dysfunctions / “injury”***
- **A shift to the idea of "rehabilitation"** is beginning
 - **A full review of techniques and goals is urgently needed**