AUTISM AND VACCINES: the TRUTH beyond the CONTROVERSY

Pediatrics on the Parkway
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AGENDA

- Brief description of diagnosis of ASDs
- The role of immunizations in ASDs
- The role of Thimerosal
- The implications in treatment

AUTISM DSM IV TR

- "Qualitative impairment in social interactions…"
- "Qualitative impairment in communication…"
- "Restricted repetitive and stereotyped patterns of behavior, interests and activities…"

SOCIAL CRITERIA DSM

- A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

1. qualitative impairment in social interaction, as manifested by at least two of the following:

a. marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction

b. failure to develop peer relationships appropriate to developmental level

c. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)

d. a lack of social or emotional reciprocity

LANGUAGE CRITERIA DSM

- qualitative impairments in communication as manifested by at least one of the following:

a. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)

b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others

c. stereotyped and repetitive use of language or idiosyncratic language

d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

BEHAVIORAL CRITERIA DSM

- restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus

b. apparently inflexible adherence to specific, nonfunctional routines or rituals

c. stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)

d. persistent preoccupation with parts of objects

"DISCLAIMERS"

Delays or abnormal functioning in at least one of the following areas, with onset before 3 years old: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

The disturbance is not better accounted for by Rett's Disorder or childhood disintegrative disorder.

ASSOCIATIONS

MEDICAL	'BEHAVIORAL'
Hypotonicity	Anxiety
Macrocephaly	Attentional issues
Tight heel cords	Cognitive issues
Seizures	Resistance to change
Metabolic/genetic issues	Sensory issues

DSM ASDs

- Autism
- Asperger's Syndrome
- Childhood Disintegrative Disorder
- Pervasive Developmental Disorder, Not Otherwise Specified
- Rett's Syndrome

THE MEDICINE MAN on the CORNER

- MMR/vaccines
- Thimerosal
- Yeast
- Gut "hypersensitivity"
- Metal toxicity
- Dietary sensitivities
- Mega-vitamins
- ….

MMR and AUTISM, LANCET 1998

- **Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children**
- ***A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith***
- **The Lancet, Volume 351, Number 9103 28 February 1998**
- ***Inflammatory Bowel Disease Study Group, University Departments of Medicine and Histopathology*** *(A J Wakefield FRCS, A Anthony MB, J Linnell PhD, A P Dhillon MRCPath, S E Davies MRCPath)* ***and the University Departments of Paediatric Gastroenterology*** *(S H Murch MB, D M Casson MRCP, M Malik MRCP, M A Thomson FRCP, J A Walker-Smith FRCP,),* ***Child and Adolescent Psychiatry*** *(M Berelowitz FRCPsych),* ***Neurology*** *(P Harvey FRCP),* ***and Radiology*** *(A Valentine FRCR),* ***Royal Free Hospital and School of Medicine, London NW3 2QG, UK***

WAKEFIELD

- **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.

WAKEFIELD

- **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.

4 of the 12 had had behavioral disorders prior to the onset of bowel dysfunction or symptoms.

One third of these 12 patients did not follow Wakefield's own hypotheses that

MMR-> bowel dysfunction->ASD

Lack of Association between Measles Virus Vaccine and Autism with Enteropathy: A Case-Control Study Jrnl PLoS ONE (9-4-08)

Mady Hornig[1*], Thomas Briese[1], Timothy Buie[2], Margaret L. Bauman[3], Gregory Lauwers[4], Ulrike Siemetzki[1], Kimberly Hummel[5], Paul A. Rota[5], William J. Bellini[5], John J. O'Leary[6], Orla Sheils[6], Errol Alden[7], Larry Pickering[8], W. Ian Lipkin[1*]

1 Center for Infection and Immunity, Mailman School of Public Health, Columbia University, New York, New York, United States of America, **2** Division of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **3** Department of Neurology, Harvard Medical School and Departments of Neurology and Pediatrics and Learning and Developmental Disabilities Evaluation and Rehabilitation Services (LADDERS), Massachusetts General Hospital, Boston, Massachusetts, United States of America, **4** Department of Pathology of Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, United States of America, **5** Measles, Mumps, Rubella, and Herpesvirus Laboratory Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, **6** Department of Histopathology, Trinity College Dublin, Dublin, Ireland, **7** American Academy of Pediatrics, Elk Grove Village, Illinois, United States of America, **8** National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America

Methodology/Principal Findings

The objective of this case-control study was to determine whether children with GI disturbances and autism are more likely than children with GI disturbances alone to have MV RNA and/or inflammation in bowel tissues and if autism and/or GI episode onset relate temporally to receipt of MMR. The sample was an age-matched group of US children undergoing clinically-indicated ileocolonoscopy. Ileal and cecal tissues from 25 children with autism and GI disturbances and 13 children with GI disturbances alone (controls) were evaluated by real-time reverse transcription (RT)-PCR for presence of MV RNA in three laboratories blinded to diagnosis, including one wherein the original findings suggesting a link between MV and ASD were reported. The temporal order of onset of GI episodes and autism relative to timing of MMR administration was examined. We found no differences between case and control groups in the presence of MV RNA in ileum and cecum. Results were consistent across the three laboratory sites. GI symptom and autism onset were unrelated to MMR timing. Eighty-eight percent of ASD cases had behavioral regression

SUBJECT CHARACTERISTIC		AUT/GI CASES	GI CONTROLS
SEX	Male	23 (92)	9 (69)
n (%)	*3–5 years*	*15*	*7*
	6–7 years	*6*	*1*
	8–10 years	*2*	*1*
	Female	2 (8)	4 (31)
	3–5 years	*0*	*1*
	6–7 years	*0*	*1*
	8–10 years	*2*	*2*
	All subjects	25 (100)	13 (100)
ETHNICITY	Caucasian	18 (72)	12 (92)
n (%)	Asian	4 (16)	0 (0)
	Hispanic	2 (8)	0 (0)
	African-American	1 (4)	1 (8)
AGE STRATUM	3–5 years	15 (60)	8 (61)
n (%)	6–7 years	6 (24)	2 (15)
	8–10 years	4 (16)	3 (23)
AGE AT BIOPSY	All subjects	5.5 (3.0)[a]	5.1 (3.0)
in years, median (IQR)			
AGE AT FIRST MMR	All subjects	15.3 (1.7)[b]	16.0 (4.9)
in months, median (IQR) [RANGE]		[12.2–22.8]	[5.6–20.5]
TIME FROM LAST MMR TO BIOPSY	All subjects	40.8 (26.7)[c]	39.8 (21.1)
in months, median (IQR) [RANGE]		[23.7–97.9]	[3.5–64.5]
TOTAL NUMBER OF MMR VACCINES	All subjects	20[d]	31
% receiving *2* doses			
TOTAL NUMBER OF ALL VACCINES	All subjects	17 (4)*	20 (1)
median (IQR) [RANGE]		[13–21]	[15–22]

[a]Mann-Whitney U, one-tailed, $P = 0.67$.
[b]Mann-Whitney U, one-tailed, $P = 0.15$.
[c]Mann-Whitney U, one-tailed, $P = 0.50$.
[d]χ^2, Fisher's exact test, one-tailed, $P = 0.36$.
[e]Mann-Whitney U, one-tailed, $P = 0.04$.

Timing of event	AUT/GI cases (n = 25)	GI controls (n = 13)
First MMR vaccine	15.3 (1.7)[a]	16.0 (4.9)
age in months, median (IQR)		
First episode of GI disturbance	12.0 (17.5)[b]	2.0 (19.5)
age in months, median (IQR)		
MMR before GI onset *[n (%)]*	12 (48)[c]	3 (23)
MMR after GI onset *[n (%)]*	13 (52)	10 (77)
Autism onset	13.5 (7.0)	Not applicable
age in months, median (IQR)		
MMR before autism onset *[n(%)]*	13 (52)	Not applicable
MMR after autism onset *[n (%)]*	12 (48)	Not applicable
GI onset before autism *[n (%)]*	16 (64)	Not applicable
GI onset after autism *[n (%)]*	9 (36)	Not applicable
MMR before GI onset *[n (%)]*	5 (20)	Not applicable
<AND>		
GI onset before autism *[n (%)]*		

Key: *MMR*, Measles-Mumps-Rubella vaccine.
[a]Mann-Whitney U, one-tailed, $p = 0.15$.
[b]Mann-Whitney U, one-tailed, $p = 0.29$.
[c]X^2, Fisher's exact test, one-tailed, $p = 0.13$.
doi:10.1371/journal.pone.0003140.t002

ORDER OF EVENTS	CASES (n = 25)	
	GI before ASD	GI after ASD
	n (%)	*n (%)*
MMR before GI	5 (31)[†]	7 (78)
MMR after GI	11 (69)	2 (22)

[†]X^2, Fisher's exact test, one-tailed, $p = 0.03$.
doi:10.1371/journal.pone.0003140.t004

Conclusions/Significance

This study provides strong evidence against association of autism with persistent MV RNA in the GI tract or MMR exposure. Autism with GI disturbances is associated with elevated rates of regression in language or other skills and may represent an endophenotype distinct from other ASD.

OTHER RECENT STUDIES SHOWING NO CAUSALITY BETWEEN MMR AND AUTISM

BRITISH MEDICAL JOURNAL Vol. 318

June, 1999 : no correlation between time of MMR (or not) with onset of autism in 498 children

NEW ENGLAND JRNL of MEDICINE

November, 2002: no correlation between MMR and autism in 500,000 Danish children

OTHER RECENT STUDIES SHOWING NO CAUSALITY BETWEEN MMR AND AUTISM

PEDIATRICS Feb., 2004

No correlation of MMR exposure to autism

JOURNAL of AUTISM and DEVELOPMENTAL DISORDERS April, 2006

No correlation of MMR exposure to autism

CDC: MMR AND AUTISM

- **MMR Vaccine Safety Research**
- Many carefully performed scientific studies have found no link between MMR vaccine and autism.

THIMEROSAL

Thimerosal breaks down to ETHYLMERCURY and Thiosalicylate

METHYL MERCURY IS TOXIC

ETHYL MERCURY IS NOT

METHYL MERCURY

Sir John Tenniel was an English Illustrator best known for his drawings in the LEWIS CARROLL books.

THIMEROSAL and VACCINES

- **PEDIATRICS Volume 112, 2003**

Anne-Marie Plesner, Peter H. Andersen and Preben B. Mortensen

Kreesten M. Madsen, Marlene B. Lauritsen, Carsten B. Pedersen, Poul Thorsen, was entitled:

Danish Population-Based Data

Thimerosal and the Occurrence of Autism: Negative Ecological Evidence From Danish Population-Based Data

PEDIATRICS Vol. 112, 2003

Results. **A total of 956 children with a male-to-female ratio of 3.5:1 had been diagnosed with autism during the period from 1971–2000. There was no trend toward an increase in the incidence of autism during that period when thimerosal was used in Denmark, up through 1990.**

From 1991 until 2000 the incidence increased and continued to rise *after* the removal of thimerosal from vaccines,including increases among children born after the discontinuation of thimerosal.

PEDIATRICS Vol. 112, 2003

Conclusions.

The discontinuation of thimerosal-containing vaccines in Denmark in 1992 was followed by an increase in the incidence of autism.

Our ecological data do not support a correlation between thimerosal-containing vaccines and the incidence of autism.

MULTI-FACTORIAL etiology of AUTISM

- GENETIC
  - FRAGILE X
  - DELETION on chromosome 21
  - DUPLICATION on chromosome 15
  - Abnormalities on chromosomes 7 + 16
- BIOCHEMICAL
  - Lesch-Nyhan
  - Smith-Lemli-Opitz
  - Phenylketonuria
- NEUROLOGIC
  - Macrocephaly
  - Neuro-migrational defects

Autism is a life-long disorder, which is characterized by a disturbance in the rate of acquisition of physical, social and language skills. It has been defined and redefined. It is perhaps the most fascinating and the most significant of the neurodevelopmental disorders.

There are multiple known (and many more unknown) causes of ASDs and thus there are multiple appropriate treatments. By identifying the ASDs early and individualizing treatment we can help our patients and their families immeasurably.

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