

A prospective study of thimerosal-containing Rho(D)-immune globulin administration as a risk factor for autistic disorders

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Abstract

Background. This study evaluated the relationship between prenatal mercury exposure from thimerosal (49.55% mercury by weight)-containing Rho(D)-immune globulins (TCRs) and autism spectrum disorders (ASDs).

Methods. The Institutional Review Board of the Institute for Chronic Illnesses approved the present study. A total of 53 consecutive non-Jewish Caucasian patients with ASDs (*Diagnostic and statistical manual of mental disorders, fourth ed.* – DSM IV) born between 1987 and 2001 who presented to the Genetic Centers of America for outpatient genetic/developmental evaluations were prospectively collected from June 1, 2005 through March 31, 2006. Imaging and laboratory testing were conducted on each patient to rule out other causal factors for their ASDs. As race-matched controls, the frequency of Rh negativity was determined from 926 non-Jewish Caucasian pregnant women who had presented for outpatient prenatal genetics care to the Genetic Centers of America between 1980 and 1989.

Results. Children with ASDs (28.30%) were significantly more likely (odds ratio 2.35, 95% confidence interval 1.17–4.52, $p < 0.01$) to have Rh-negative mothers than controls (14.36%). Each ASD patient's mother was determined to have been administered a TCR during her pregnancy.

Conclusion. The results provide insights into the potential role prenatal mercury exposure may play in some children with ASDs.

Keywords: *Developmental delay, ethylmercury, rhogam, thimerosal, thiomersal*

Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movement patterns, and sensory dysfunction [1,2]. While genetic factors are recognized as being important in the pathogenesis of ASDs, a role for environmental factors has received considerable attention. For example, Beversdorf et al. reported that pathological changes in the cerebellum in autism are thought to correspond to an event before 30–32 weeks of gestation [3]. These researchers determined that a higher incidence of prenatal stressors was found in autism at 21–32 weeks of gestation, with a peak at 25–28 weeks, and concluded that their data supported the possibility of prenatal stressors as a potential contributor to autism. Additionally, researchers reported that exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions

similar to traits defining or associated with autistic disorders, and that these similarities extend to neuroanatomy, neurotransmitters, and biochemistry [4–7].

Rho(D)-immune globulin is an immune globulin preparation containing antibodies to Rho(D) that is intended for intramuscular injection. Prior to late 2002/early 2003 when the last doses of thimerosal-containing Rho(D)-immune globulin preparations expired, most formulations of Rho(D)-immune globulin contained thimerosal. Thimerosal is an ethylmercury-containing compound (49.55% mercury by weight) that was added to Rho(D)-immune globulin preparations at the preservative level of 0.003–0.01%. Rho(D)-immune globulin is used to prevent isoimmunization in the Rho(D)-negative individual exposed to Rho(D) positive blood as a result of fetomaternal hemorrhage occurring during delivery of an Rho(D) positive infant, abortion (either spontaneous or induced), or following amniocentesis or abdominal trauma. Rh hemolytic

disease of the newborn is the result of the active immunization of a Rho(D)-negative mother by Rho(D) positive red cells entering the maternal circulation during a previous delivery, abortion, amniocentesis, abdominal trauma, or as a result of red cell transfusion [8,9]. Rho(D)-immune globulin acts by suppressing the immune response of Rho(D)-negative individuals to Rho(D) positive red blood cells. The mechanism of action of Rho(D)-immune globulin is not fully understood.

Historically, Rho(D)-immune globulin was administered within 72 hours of a full-term delivery of a Rho(D) positive infant by a Rho(D)-negative mother or following known potential exposure between maternal and fetal blood. It was observed that administration of Rho(D)-immune globulin under such guidelines reduced the incidence of Rh isoimmunization from 12–13% to 1–2% [10]. It was reported that the 1–2% of treatment failures that continued to occur probably resulted from isoimmunization occurring during the latter part of pregnancy or following pregnancy [11]. Bowman and Pollock showed that the incidence of isoimmunization could be further reduced from approximately 1.6% to less than 0.1% by administering Rho(D)-immune globulin preparations in two doses, one antenatal at 28 weeks of gestation and another following delivery [12]. As a result, in the late 1980s/early 1990s, at the same time that epidemic increasing trends in neurodevelopmental disorders were first observed in the USA, the American College of Obstetricians and Gynecologists had adopted the recommendation that in addition to birth and times of potential mixing of fetal and maternal blood, Rho(D)-immune globulin preparations should be routinely administered to all Rh-negative mothers at 28 weeks of gestation [13].

This study focuses on prenatal mercury exposure from thimerosal-containing Rho(D)-immune globulin preparations. The purpose of the present study was to determine whether or not the epidemiological evidence suggests a relationship exists between prenatal mercury exposure from thimerosal-containing Rho(D)-immune globulin preparations and the development of ASDs.

Materials and methods

The Institutional Review Board of the Institute for Chronic Illnesses (Office for Human Research Protections, US Department of Health and Human Services IRB number: IRB00005375) approved the present study.

Patients

Consecutive non-Jewish Caucasian patients with ASDs who prospectively presented to the Genetic

Centers of America for outpatient genetic/developmental evaluations from June 1, 2005 through March 31, 2006 were examined. Each patient was previously diagnosed with an ASD based upon the *Diagnostic and statistical manual of mental disorders, fourth ed.* (DSM-IV) criteria. A total of 53 patients with ASDs were identified who were born between 1987 and 2001. Table I summarizes the overall profile of the patients with ASDs examined in the present study. Each patient was tested to rule out brain structural abnormalities (CT or MRI head scans) and vision and hearing abnormalities. Additionally, laboratory testing was conducted on each patient, and all were determined to be negative for fragile X syndrome, chromosomal abnormalities (structural and numeric), subtelomere chromosome rearrangements, thyroid function abnormalities, Prader-Willi syndrome/Angelman syndrome, urine organic acid abnormalities, polychlorinated biphenyl/pesticide exposure, and Rett syndrome (LabCorp).

Evaluation

A complete family and medical history and a review of the patient's medical records were undertaken for each patient examined in the present study. Each patient in the present study had information collected regarding the Rh status of the mother and regarding the injection of the mother with thimerosal-containing Rho(D)-immune globulin preparations during pregnancy.

Controls

In order to evaluate the non-Jewish Caucasian frequency of Rh negativity, the Rh status of 926 non-Jewish Caucasian pregnant women who presented for outpatient prenatal genetics care to the Genetic Centers of America between 1980 and 1989 was determined by review of the patient's medical records. A total of 133 of these women were determined to be Rh-negative.

Statistical analyses

In the present study, the statistical package contained in StatsDirect™ (Version 2.4.2) was employed. A 2×2 contingency table was used to evaluate the relative frequency of maternal Rh negativity in non-Jewish Caucasian patients examined with ASDs in comparison to the non-Jewish Caucasian control group. The Fisher's exact test statistic was utilized to determine statistical significance. A two-tailed p value of <0.05 was considered statistically significant.

Results

Table II summarizes the frequency of maternal Rh negativity in non-Jewish Caucasian patients with ASDs in comparison to a non-Jewish Caucasian control group. It was observed that the maternal Rh negativity in non-Jewish Caucasian patients with ASDs was 28.30% and in the non-Jewish Caucasian control group was 14.36%. It was determined that the frequency of maternal Rh negativity was significantly increased (odds ratio 2.35, 95% confidence interval 1.17–4.52, $p < 0.01$) in non-Jewish Caucasian patients with ASDs in comparison to the non-Jewish Caucasian control group. The chart

Table I. Profile of patients with autism spectrum disorders who presented for outpatient care to the Genetic Centers of America from June 1, 2005 through March 31, 2006.

	Autism spectrum disorder group
Number of males/females (ratio)	48/5 (9.6:1)
Median age in years (range)	9 (3–18)
Median year of birth (range)	1997 (1987–2001)
Number of children with autism (%)	33 (62%)
Number of children with pervasive developmental delay – not otherwise specified (%)	20 (38%)
Residence*	
Northeast	17%
Midwest	19%
Mountain/Plains/South Central	4%
Southeast	49%
West	11%

*Midwest: IA, IL, IN; Mountain/Plains/South Central: KS, TX; Northeast: MA, NH, NJ, PA; Southeast: FL, MD, NC, SC, VA; West: CA, WA.

Table II. A summary of the frequency of maternal Rh negativity in patients with autistic disorders in comparison to the control group.

	Frequency of maternal Rh negativity
Autism spectrum disorders group* (n)	28.30% (15/53)
Control group** (n)	14.36% (133/926)
Odds ratio	2.35
p Value [†]	<0.01
95% confidence interval	1.17–4.52

*Autism spectrum disorders included children diagnosed with autism or 'pervasive developmental delay – not otherwise specified'. All the patients with Rh-negative mothers were exposed to thimerosal from Rho(D) immune globulin preparations their mother received while pregnant. **The control group frequency of Rh negativity was determined from pregnant non-Jewish Caucasian women who presented for outpatient prenatal genetics care to the Genetic Centers of America. [†]The Fisher's exact test statistic (two-tailed p value) was employed to determine statistical significance.

review of the patients with ASDs revealed that each patient's mother was administered a thimerosal-containing Rho(D)-immune globulin preparation during her pregnancy (one patient's mother was administered two during her pregnancy).

Discussion

In the present study, an examination of the relationship between Rho(D)-immune globulin administration and the risk of developing ASDs was undertaken. It was observed that patients with ASDs were significantly more likely to have mothers who were Rh-negative than a race-matched control group. It was also observed that each patient with an ASD whose mother was Rh-negative received at least one thimerosal-containing Rho(D)-immune globulin injection during her pregnancy.

In considering the patients evaluated in the present study, consecutive patients with ASDs who prospectively presented to the Genetic Centers of America for genetic/developmental evaluations were examined. These patients were not aware at the time of initial clinical presentation that information was going to be collected regarding maternal Rh-negative status or prenatal thimerosal-containing Rho(D)-immune globulin exposure as part of their evaluation by the Genetic Centers of America. In examining these ASD patients, identifiable alternate causes for their ASDs were excluded. The patients with ASDs represented a single racial group, which minimized potential racial differences in the rate of Rh negativity. The control group examined in the present study was matched to the ASD group, so that the control group was comprised only of non-Jewish Caucasians. The control group was derived from pregnant women who presented to the Genetic Centers of America for outpatient prenatal genetics care, and hence it was of integral importance to the management of each patient's pregnancy to determine their Rh status.

The maternal rate of Rh negativity observed in the present study (14.36%) is consistent with rates observed by researchers in several other similar populations including Lurie et al. (8.6%) and Holmes et al. (9%) [14,15], but is slightly higher. This may be a reflection of the fact that the control group in the present study was comprised only of non-Jewish Caucasians, whereas these other studies may have had racially mixed control groups.

Holmes et al. observed that the mothers of autistic children had a significantly increased frequency of Rh negativity (46% vs. 9%) in comparison to non-affected controls, which is consistent with observations made in the present study [15]. These same researchers showed that mothers of autistic children were injected with significantly more

Rho(D)-immune globulin preparations during pregnancy than non-affected controls [15]. Other researchers have also implicated a role for prenatal mercury exposure from the administration of thimerosal-containing Rho(D)-immune globulin preparations in ASDs [16–18].

The biological plausibility of the present findings are supported by the effects, previously reported by Faustman et al. of mercury on neuronal development: "...mercury exposure altered cell number and cell division; these impacts have been postulated as modes of action for the observed adverse effects in neuronal development. The potential implications of such observations are evident when evaluated in context with research showing that altered cell proliferation and focal neuropathologic effects have been linked with specific neurobehavioral deficits (e.g., autism)" [19]. It has also been shown that mercury exposure can trigger a biochemical cyclical pattern of interaction to develop that is directly characteristic with the biochemistry observed in some ASDs, and would be expected to correlate with the behavioral/physical traits associated with or defining ASDs [20]. Additionally, it has been observed in previous human poisoning with mercury that there is a significant association between prenatal/postnatal mercury exposure and delayed motor development, delayed language development, learning disabilities, attention deficits, and autism [21–24].

Studies into the mercury kinetics of prenatal/postnatal thimerosal administration have shown that the ethylmercury from thimerosal is capable of crossing the placental and blood–brain barriers and results in appreciable persistent bound inorganic mercury content in tissues including the brain [25–29]. Moreover, it has been reported in prenatal animal studies that ethylmercury compounds very readily pass through the placental barrier (to a greater extent than the corresponding methylmercury compound) [30]. It has also been shown that exposure to ethylmercury results in a greater mercury concentration in fetal tissues than the mother, especially in the fetal central nervous system [31]. In examining the retention of mercury in tissues, it has been shown that the half-life for organic mercury in the brain is 14 days and that the half-life for the significant inorganic fraction of mercury in the brain is immeasurable (>120 days), observed following injection of thimerosal into infant monkeys using an administration schedule that mimicked the US vaccine schedule of the 1990s (weight- and age-adjusted) [26].

Furthermore, it has been shown that administration of prenatal thimerosal to animals can induce significant fetal lethality and teratogenicity in a dose-dependent fashion [27,32,33]. Heinonen et al. examined 2277 children with birth defects among 50 282 mother–child pairs and determined that thimerosal exposure during the first 4 months of pregnancy

was associated with a significantly ($p < 0.05$) increased risk (survival and race standardized relative risk = 2.69) of birth defects [34]. Hornig et al. administered thimerosal to mice, mimicking the US routine childhood immunization schedule of the 1990s (weight- and age-adjusted), and observed autistic symptoms in a susceptible mouse strain that included growth delay, reduced locomotion, exaggerated response to novelty, increased brain size, decreased numbers of Purkinje cells, significant abnormalities in brain architecture affecting areas subserving emotion and cognition, and densely packed hyperchromic hippocampal neurons with altered glutamate receptors and transporters [35]. In 2004, thimerosal was recognized by the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment as a developmental toxin, meaning that it can cause birth defects, low birth weight, biological dysfunctions, or psychological or behavior deficits that become manifest as the child grows, and that maternal exposure during pregnancy can disrupt the development or even cause the death of the fetus.

In a series of molecular studies with neurons it was recently shown that nanomolar (nM) to micromolar (μ M) concentrations of thimerosal are capable of inducing neuronal death, neurodegeneration, membrane damage, and DNA damage within hours of exposure [36–44]. Additionally, it has also been shown that nM to μ M concentrations of thimerosal are capable of disrupting critical signaling pathways/biochemical events necessary for neurons to undergo normal neuronal development [45–47].

Conclusion

It is clear from these data, and other emerging data that have recently been published, that additional neurodevelopmental disorder research should be undertaken in the context of evaluating mercury-associated exposures, especially from thimerosal-containing Rho(D)-immune globulins administered during pregnancy. Further studies should also be undertaken in additional databases/registries to assess the compatibility of the present results with trends in neurodevelopmental disorders in other US populations, and to observe whether thimerosal-containing Rho(D)-immune globulins are associated with other birth defects in children. If administration of thimerosal-containing Rho(D)-immune globulins during pregnancy has contributed significantly to the US neurodevelopmental disorder epidemic, then, since thimerosal has been removed from Rho(D)-immune globulins since the early 2000s, one may predict that the rate of new cases of neurodevelopmental disorders will begin to significantly decline over the next few years.

Potential conflict of interest: David Geier has been a consultant in cases involving vaccines/biologics before the no-fault National Vaccine Injury Compensation Program and in civil litigation. Dr Mark Geier has been an expert witness and consultant in cases involving vaccines/biologics before the no-fault National Vaccine Injury Compensation Program and in civil litigation.

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