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Acetaminophen (paracetamol) use, measles-mumps-rubella vaccination, and autistic disorder

The results of a parent survey

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ABSTRACT The present study was performed to determine whether acetaminophen (paracetamol) use after the measles-mumps-rubella vaccination could be associated with autistic disorder. This case-control study used the results of an online parental survey conducted from 16 July 2005 to 30 January 2006, consisting of 83 children with autistic disorder and 80 control children. Acetaminophen use after measles-mumps-rubella vaccination was significantly associated with autistic disorder when considering children 5 years of age or less (OR 6.11, 95% CI 1.42–26.3), after limiting cases to children with regression in development (OR 3.97, 95% CI 1.11–14.3), and when considering only children who had post-vaccination sequelae (OR 8.23, 95% CI 1.56–43.3), adjusting for age, gender, mother's ethnicity, and the presence of illness concurrent with measles-mumps-rubella vaccination. Ibuprofen use after measles-mumps-rubella vaccination was not associated with autistic disorder. This preliminary study found that acetaminophen use after measles-mumps-rubella vaccination was associated with autistic disorder.

KEYWORDS *acetaminophen; autism; paracetamol; vaccination*

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Introduction

Autistic disorder (AD) is a severe developmental disorder defined by social and communication deficits and ritualistic-repetitive behaviors that are seen in early childhood (American Psychiatric Association, 1994). A small percentage of cases of AD are associated with several known congenital conditions such as fragile X syndrome, Angelman syndrome, tuberous sclerosis, congenital rubella syndrome, neurofibromatosis, phenylketonuria, and Rett syndrome (Fombonne, 1999). Approximately 94 percent of AD cases are not associated with a congenital condition and have an unknown etiology (Fombonne, 1999). AD is a neurobiological disorder with genetic underpinnings (Muhle et al., 2004), and recent evidence suggests that brain growth abnormalities and symptoms may occur during the first year of life (Courchesne et al., 2003).

For some children, environmental factors may contribute to an increased risk of AD (Lawler et al., 2004). Theories about possible environmental triggers for AD include childhood vaccinations, environmental exposures, and viral infections (Hertz-Picciotto et al., 2006). Our previous ecological study suggested a link between acetaminophen use and AD (Schultz et al., submitted). Small clinical studies have suggested a link between measles-mumps-rubella (MMR) vaccination and AD (Furlano et al., 2001; Singh and Jensen, 2003; Singh et al., 2002; Torrente et al., 2002; Uhlmann et al., 2002; Wakefield et al., 1998; 2000; but see Horton, 2004; Murch et al., 2004; Taylor et al., 2002). However, epidemiological studies have not supported the relationship between prevalence of AD and the MMR vaccine (Fombonne and Chakrabarti, 2001; Institute of Medicine, 2001). A prospective study from Finland showed no association between the MMR vaccination and AD (Peltola et al., 1998), and two large population studies from Denmark and England also showed no evidence for this association (Madsen et al., 2002; Taylor et al., 1999). A further study from England found no significant increase in AD following the introduction of the MMR vaccination (Chen et al., 2004), and comparison of MMR vaccination coverage in California with AD also showed no association (Dales et al., 2001).

Reported adverse reactions in children to the MMR vaccination are fever (5–15%) and rash (5%), although other complications are rare (CDC, 2006). Some other factor related to the MMR vaccination or the timing of the MMR vaccination may be related to AD. Acetaminophen (also called paracetamol) is often given to prevent or treat a reaction to the MMR vaccination. Some low-functioning children with AD have been shown to have a sulfation deficit which causes them to process acetaminophen differently from control children (Alberti et al., 1999). A search of the literature revealed no studies investigating a link between acetaminophen use and

AD, other than our ecological study (Schultz et al., submitted). The present study was initiated to assess whether acetaminophen use after MMR vaccination could be associated with AD. This study was approved by the University of California, San Diego Human Research Protections Program and the Institutional Review Board at San Diego State University.

Materials and methods

Parents of children with and without AD were recruited via the Internet to take an Internet-based survey. Participants were invited to complete either a 36-question version for children with AD (case children) or a 21-question version for children without AD (control children). Two autism listserv publications, Valerie's List (ValeriesList@aol.com) and the Schafer Autism Report (http://www.sarnet.org), published links to the online surveys. These publications are generic in nature and unlikely to attract a biased response group. Advertisements were also placed online using Google™, and individuals who performed online searches containing keywords (autistic, autism etc.) were shown advertisements requesting their participation in a research survey. The number of keywords used was 306, and they can be grouped into the following categories: autism and autistic features (262), treatment for autism (24), prominent people involved in autism (13), and possible causes of autism (7).

Cases were obtained by sending requests for participation to Valerie's List and the Schafer Autism Report beginning on 16 July 2005. This was followed by Google™ advertising beginning on 22 September 2005. A total of 190 case surveys were completed by 16 October 2005.

The controls were obtained in four separate groups. The parents of children with AD who took the survey between 16 July 2005 and 21 September 2005 were asked to provide a control for their survey. Nine control surveys were obtained in this way. From 22 September 2005 to 16 October 2005, parents for the control survey were solicited using Google™ advertising which yielded an additional 41 control surveys. On 30 November 2005 an additional appeal was made via Valerie's List to parents who had taken the case survey to find parents to take the control survey. This resulted in an additional 23 control surveys. On 7 January 2006 another appeal was made via Valerie's List and advertisements were again placed on Google™. By 30 January 2006, 50 additional control surveys had been obtained for a total of 123. Parents of case children recruited via Valerie's List and the Schafer Autism Report were asked to find parents unrelated to them to take the control surveys. Parents of control children recruited via Google™ would most likely be unrelated to the parents who took the case surveys. We

requested that parents not take the control survey if their child had autism or developmental problems.

Parents taking the case survey were asked to select the diagnosis for their child from the following choices: autism or autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), Asperger's disorder, or other. Limiting the age of children in both groups to less than 18 years, the case diagnosis to autism or autistic disorder, and the respondents to parents, yielded 114 case and 113 control surveys. All of the parents of case children reported that their child was diagnosed by at least one medical professional, most commonly a clinical psychologist ($n = 61$), while others reported a diagnosis from a neurologist ($n = 33$), pediatrician ($n = 33$), child psychiatrist ($n = 18$), or developmental pediatrician ($n = 11$).

The MMR vaccination is recommended for children aged 12 to 15 months. Since children less than 1 year old would not have had the opportunity to have this vaccination, the study was further limited to children older than 1 year at the time of the study. This yielded 113 case and 109 control surveys. The main question of interest in this study was whether children had been given acetaminophen after the MMR vaccination. After restricting the study to those who answered this question, 83 case and 80 control children were available for study. Compared to those retained in the study, those dropped were slightly older (8.2 versus 7.5 years) and more likely to be male (81% versus 68%). Caucasian ethnicity of the mothers and fathers for those dropped was 85 and 83 percent, respectively, which was similar to the mothers and the fathers of those retained, 85 and 84 percent, respectively. Analysis with 113 case and 109 control surveys did not significantly change the findings of the study.

Three cases reported first diagnosis before the age of 20 months. A total of 12 cases were first diagnosed before the age of 24 months, 52 cases were diagnosed from 24 through 36 months of age, and 19 between ages 3 and 18 years. Fifty-four cases reported that their child had been given one or more standardized diagnostic tests (Autism Diagnostic Interview–Revised, Autism Diagnostic Observation Schedule, Childhood Autism Rating Scale etc.) while 20 cases reported that they did not know what specific test had been used as part of a clinical evaluation, and nine cases did not respond to the question.

The surveys included questions on the child's gender, ethnicity and education of each respondent parent (five choices each), the date of the child's birth, and the nature of the child's development. On the survey, parents were also asked whether their child was given an analgesic to prevent or treat a reaction to the MMR vaccination. Parents could check yes or no to the use of aspirin, acetaminophen, or ibuprofen, in that order. No parents reported using aspirin and this variable was dropped from further analysis. Parents were also asked in a separate question whether their child

was given aspirin (yes, no), acetaminophen (yes, no) or ibuprofen (yes, no) during the ages of 12 to 18 months. For this question as well, no parents reported using aspirin; only use of acetaminophen and ibuprofen were explored.

The survey asked parents if their child appeared sick (yes, no) at the time he/she was given the MMR vaccination. The survey also included a question asking whether their child had any of the following reactions to the MMR vaccination: fever, rash, diarrhea, irritability, and/or seizures. These are the complications of the MMR vaccination as reported by the CDC (2006). The total number of reactions to the MMR vaccination was recoded into a new variable.

Parents of autistic children were questioned about the nature of their child's development to determine if the child had a regression in development. Autistic regression indicates that a child goes through a normal period of development followed by a regression in development and subsequent development of AD. For the purpose of this study, regression was defined as a child's attainment and loss of at least three words, using the definition of Lord and colleagues (2004).

SAS for Windows version 9.1 was used for all statistical analyses. Logistic regression analysis and 2×2 contingency tables were used to test the univariate association of AD with acetaminophen or ibuprofen use after MMR vaccination, acetaminophen or ibuprofen use at age 12 to 18 months, age, gender, education of the parents, ethnicity of the parents, whether the child appeared sick concurrent with the MMR vaccination (i.e. illness apparent prior to the vaccination), and the number of sequelae to the MMR vaccination.

Adjusted logistic regression analysis was used to produce models of AD with acetaminophen use, ibuprofen use, and the presence of illness concurrent with the MMR vaccination, adjusting for variables found to be associated with AD ($p < 0.05$) in univariate analyses if they produced a 10 percent change in the odds ratio. Additional logistic regression models were developed for subgroups of the sample. One subgroup was limited to children 1 to 5 years old in order to minimize the effect of recall bias. An additional subgroup included only case children with regression because these children may be more likely to have been affected by environmental influences. A further subgroup was limited to children who had sequelae to the MMR vaccination in order to test whether acetaminophen use after MMR vaccination was a surrogate measure for post-vaccination sequelae. Since children with post-vaccination sequelae are more likely to be given acetaminophen, this analysis was included to test whether acetaminophen use was associated with AD while holding the variable for post-vaccination sequelae constant.

Interaction analyses were also performed to determine if the association of AD with acetaminophen use after MMR vaccination, acetaminophen use age 12 to 18 months, and illness concurrent with the MMR vaccination varied by the levels of the adjustment variables.

Results

Table 1 presents the characteristics of children in the AD research survey. The mean age of cases (n = 83) and controls (n = 80) was similar at 7.7 years and 7.3 years, respectively ($p = 0.53$). Gender varied by group; 86 percent of the cases were male versus 50 percent of the controls ($p < 0.01$). There were no apparent differences between the two groups in terms of parent

Table 1 **Characteristics of participants in the autistic disorder survey, 2005–6**

Variable (n = cases, controls)	*Cases (N = 83)*	*Controls (N = 80)*	*p-value*[a]
Age: mean (SD) (years) (83, 80)	7.7 (4.1)	7.3 (3.9)	0.527[b]
No. sequelae to MMR: mean (SD) (80, 75)	1.3 (1.3)	0.4 (0.7)	**<0.001**[b]
	% (n)	*% (n)*	
Gender: male (83, 80)	86 (71)	50 (40)	**<0.001**
Mother's ethnicity: Caucasian (83, 79)	78 (65)	92 (73)	**0.012**
Father's ethnicity: Caucasian (83, 80)	87 (72)	81 (65)	0.338
Mother's education: college graduate or higher (82, 79)	61 (50)	65 (51)	0.639
Father's education: college graduate or higher (81, 79)	53 (43)	61 (48)	0.278
Parental report of regression: loss of words (81, n/a)	38 (31)		
Cases having sibling with autism (83, n/a)	12 (10)		
Received MMR (83, 80)	100 (83)	99 (79)	0.491[c]
Presence of illness concurrent with MMR (81, 80)	31 (25)	4 (3)	**<0.001**
Reported sequelae to MMR (80, 75):			
Fever	53 (42)	21 (16)	**<0.001**
Rash	11 (9)	4 (3)	0.091
Diarrhea	24 (19)	1 (1)	**<0.001**
Irritability	40 (32)	12 (9)	**<0.001**
Seizures	1 (1)	0 (0)	0.516[c]
Any of above	59 (47)	28 (21)	**<0.001**
Acetaminophen use after MMR (83, 80)	75 (62)	55 (44)	**0.008**
Ibuprofen use after MMR (53, 58)	15 (8)	9 (5)	0.379[c]
Acetaminophen use age 12–18 months (69, 68)	94 (65)	75 (51)	**0.002**
Ibuprofen use age 12–18 months (49, 54)	61 (30)	52 (28)	0.338

MMR: measles-mumps-rubella vaccination.
[a] All *p*-values by chi-square unless otherwise noted; bold type denotes significance.
[b] Logistic regression *p*-value.
[c] Fisher's exact test *p*-value, two-sided.

education or ethnicity of the fathers, but more mothers of controls were Caucasian (92% versus 78%, $p = 0.01$).

Presence of illness concurrent with MMR vaccination varied by group (cases 31%, controls 4%, $p < 0.01$). Sequelae to the MMR vaccination were reported more frequently for the cases than controls: fever (53% versus 21%, $p < 0.01$), rash (11% versus 4%, $p = 0.09$), diarrhea (24% versus 1%, $p < 0.01$), irritability (40% versus 12%, $p < 0.01$), and seizures (1% versus 0%, $p = 0.52$). Overall, 59 percent of the cases compared with 28 percent of the controls experienced at least one of these sequelae ($p < 0.01$).

Acetaminophen use after MMR vaccination ($n = 163$) varied by group, with significantly more cases than controls reporting its use (75% versus 55%, $p < 0.01$). Acetaminophen use at age 12 to 18 months ($n = 137$) also varied significantly by group, with more cases than controls reporting its use (94% versus 75%, $p < 0.01$). More cases than controls reported using ibuprofen after MMR vaccination ($n = 111$, 15% versus 9%) and at age 12 to 18 months ($n = 103$, 61% versus 52%), although these differences were not significant. Analgesic use for acetaminophen and ibuprofen was recorded as yes/no and includes overlap for individuals taking both drugs ($n = 6$ for individuals using both analgesics after MMR vaccination and $n = 55$ for individuals using both analgesics at age 12 to 18 months).

The analyses were limited to those parents who answered the question on acetaminophen use after MMR vaccination ($n = 163$ surveys). Since responses to the other questions varied, the numbers answering each question are shown in parentheses. Assuming non-responses were 'No' changed the significance level of acetaminophen use at 12 to 18 months from $p < 0.01$ to $p < 0.05$, but did not alter the lack of significance for ibuprofen use after the MMR vaccination or at age 12 to 18 months.

Table 2 shows the crude associations of potential risk factors with AD. Males were significantly more likely to have AD ($n = 163$, OR 5.92, 95% CI 2.79–12.6). Parents' education, fathers' ethnicity, and children's age were not significantly associated with AD. Children with illness concurrent with measles-mumps-rubella vaccination were more than 11 times as likely to have AD ($n = 161$, OR 11.5, 95% CI 3.30–39.8). For each sequela to the MMR vaccination, children were twice as likely to have AD ($n = 155$, OR 2.36, 95% CI 1.64–3.42). Use of acetaminophen after MMR vaccination ($n = 163$, OR 2.42, 95% CI 1.25–4.69) and at age 12 to 18 months ($n = 137$, OR 5.42, 95% CI 1.72–17.1) significantly increased the likelihood of being in the AD group by two and five times, respectively. Ibuprofen use after MMR vaccination and at age 12 to 18 months was not significantly associated with AD.

Table 3 presents the associations of analgesic use between 12 and 18 months of age with autistic disorder adjusted for age, gender and mother's

Table 2 **Crude associations with autistic disorder, 2005–6**

Variable[a]	*Odds ratio*	*95% CI*	*p-value*[b]
Age: per year (163)	1.03	0.95–1.11	0.527
Gender: male/female (163)	5.92	2.79–12.6	**<0.001**
Mother's ethnicity: Caucasian/other (162)	0.30	0.11–0.79	**0.015**
Father's ethnicity: Caucasian/other (163)	1.51	0.65–3.52	0.340
Mother's education: college graduate or higher/other (161)	0.86	0.45–1.63	0.639
Father's education: college graduate or higher/other (160)	0.73	0.39–1.37	0.328
Presence of illness concurrent with MMR: yes/no (161)	11.5	3.30–39.8	**<0.001**
No. sequelae to MMR: per sequela (155)	2.36	1.64–3.42	**<0.001**
Acetaminophen use after MMR: yes/no (163)	2.42	1.25–4.69	**0.009**
Ibuprofen use after MMR: yes/no (111)	1.88	0.58–6.17	0.295
Acetaminophen use age 12–18 months: yes/no (137)	5.42	1.72–17.1	**0.004**
Ibuprofen use age 12–18 months: yes/no (103)	1.47	0.67–3.21	0.339

MMR: measles-mumps-rubella vaccination.
[a] Brackets show number of respondents to the question out of a possible 163.
[b] Bold type denotes significance.

ethnicity. Although age was not a confounder of the associations, it was included in the final models for completeness. Children who used acetaminophen at age 12 to 18 months were more than eight times as likely to be in the AD group when all children were considered (n = 137, OR 8.37, 95% CI 2.08–33.7) and more than 20 times as likely to be in the AD group when limiting cases to children with regression (n = 93, OR 20.9, 95% CI 1.33–329). Limiting the analysis to all children from 1 to 5 years produced

Table 3 **Adjusted[a] associations of analgesic use age 12–18 months with autistic disorder, 2005–6**

Variable (n = cases, controls)	*Odds ratio*	*95% CI*	*p-value*[b]
Children 1–18 years			
Acetaminophen (70, 67)	8.37	2.08–33.7	**0.003**
Ibuprofen (49, 53)	2.17	0.82–5.72	0.119
Children 1–5 years			
Acetaminophen (23, 23)	5.29	0.99–28.3	0.052
Ibuprofen (16, 19)	1.23	0.22–6.85	0.810
Children 1–18 years, cases limited to children with regression			
Acetaminophen (26, 67)	20.9	1.33–32.9	**0.031**
Ibuprofen (20, 53)	2.44	0.63–9.54	0.199

[a] Adjusted for age, gender, and mother's ethnicity.
[b] Bold type denotes significance.

a marginally significant association of acetaminophen use at 12 to 18 months with AD (n = 46, p = 0.052). Ibuprofen use at age 12 to 18 months was not significantly associated with AD when all children were considered (n = 102), when considering children 1 to 5 years (n = 35), or when limiting cases to children with regression (n = 73). The lack of an association remained when limiting the analysis of ibuprofen use to children who did not report taking acetaminophen (data not shown in table).

Table 4 shows the association of presence of illness concurrent with MMR vaccination and AD, adjusted for age, gender, mother's ethnicity, and acetaminophen use after measles-mumps-rubella vaccination. Children with illness concurrent with the MMR vaccination were more than eight times as likely to be in the AD group when all children were considered (n = 160, OR 8.81, 95% CI 2.29–33.9), and more than 17 times as likely to be in the AD group when cases were limited to children with regression in development (n = 108, OR 17.2, 95% CI 3.51–84.5). There was no significant association between illness concurrent with the MMR vaccination and AD when considering children 1 to 5 years old (n = 52).

Table 5 presents the association of analgesic use after MMR vaccination with AD, adjusted for age, gender, mother's ethnicity, and the presence of illness concurrent with the MMR vaccination. Acetaminophen use after MMR vaccination was associated with an increase of sixfold in the likelihood of AD when considering only children 1 to 5 years (n = 52, OR 6.11, 95% CI 1.42–26.3), fourfold after limiting cases to children with regression in development (n = 108, OR 3.97, 95% CI 1.11–14.3), and eightfold when considering only children who had post-vaccination sequelae (n = 67, OR 8.23, 95% CI 1.56–43.3). The association of acetaminophen use after MMR vaccination with AD was marginally significant when considering all children 1 to 18 years (n = 180, p = 0.059). Ibuprofen use after MMR vaccination was not significantly associated with AD for children 1 to 18 years (n = 108), for children 1 to 5 years (n = 39), when cases

Table 4 **Adjusted[a] associations for the presence of illness concurrent with measles-mumps-rubella vaccination and autistic disorder, 2005–6**

Variable (n = cases, controls)	*Odds ratio*	*95% CI*	*p-value*[b]
Children 1–18 years (81, 79)	8.81	2.29–33.9	**0.002**
Children 1–5 years (26, 26)	3.35	0.40–28.0	0.265
Children 1–18 years, cases limited to children with regression (29, 79)	17.2	3.51–84.5	**<0.001**

[a] Adjusted for age, gender, mother's ethnicity, and acetaminophen use after measles-mumps-rubella vaccination.
[b] Bold type denotes significance.

Table 5 **Adjusted[a] associations of analgesic use after measles-mumps-rubella vaccination with autistic disorder, 2005–6**

Variable (n = cases, controls)	*Odds ratio*	*95% CI*	*p-value[b]*
Children 1–18 years			
Acetaminophen (81, 79)	2.13	0.97–4.66	0.059
Ibuprofen (51, 57)	1.62	0.34–7.73	0.544
Children 1–5 years			
Acetaminophen (26, 26)	6.11	1.42–26.3	**0.015**
Ibuprofen (18, 21)	3.60	0.45–28.7	0.226
Children 1–18 years, cases limited to children with regression			
Acetaminophen (29, 79)	3.97	1.11–14.3	**0.035**
Ibuprofen (19, 57)	1.72	0.21–14.5	0.615
Children 1–18 years with post-vaccination sequelae			
Acetaminophen (46, 21)	8.23	1.56–43.3	**0.013**
Ibuprofen (26, 14)	0.89	0.10–8.30	0.918

[a] Adjusted for age, gender, mother's ethnicity, and acetaminophen use after measles-mumps-rubella vaccination.
[b] Bold type denotes significance.

were limited to children with regression ($n = 76$), or for children with post-vaccination sequelae ($n = 40$).

Acetaminophen use after MMR vaccination was tested for interaction with the number of post-vaccination sequelae and with the presence of concurrent illness at the time of the MMR vaccination. No significant interactions were found in these analyses ($p > 0.05$).

Discussion

The present study found that acetaminophen use after the MMR vaccination was associated with AD when considering children 1 to 5 years, after limiting cases to children with regression in development, and when considering only children who had post-vaccination sequelae. This finding could explain the inconsistency of the previous studies of MMR and AD since acetaminophen use was not considered.

Acetaminophen use at age 12 to 18 months was also significantly associated with AD. Since MMR vaccination is usually given at age 12 to 15 months, this finding would be expected if the combination of MMR vaccination and acetaminophen use is a risk factor for AD. Ibuprofen use at age 12 to 18 months was not associated with AD. This indicates that the use of analgesics after MMR vaccination associated with AD may be specific for

acetaminophen. However, fewer parents reported ibuprofen use and this study should be repeated with larger numbers of ibuprofen users.

The analysis of acetaminophen use after MMR vaccination included limiting cases to children with regression in development since it was thought that these children may develop normally until their MMR vaccination. The odds ratio for acetaminophen use (versus none) after MMR vaccination attained significance after limiting cases to children with regression (OR 3.97, 95% CI 1.11–14.3). This result is consistent with the possibility that regression (and subsequent AD) is due to the administration of acetaminophen after MMR vaccination.

This study found that illness concurrent with the MMR vaccination was significantly associated with AD when considering all children 1 to 18 years old and after limiting cases to children with regression in development. The odds ratio of the association was higher when considering only children with regression in development (OR 17.2 versus 8.81). It is possible that children with illness concurrent with the MMR vaccination would have a weakened immune system due to the presence of illness, and this could have predisposed them to developing AD. However, it is also possible that more children with AD were reported to be ill at the time of their MMR vaccination because symptoms of AD could have been interpreted as illness, or parents could have reported post-vaccination sequelae as concurrent illness. Illness at the time of the MMR vaccination should be investigated further as a risk factor for AD. Currently the CDC (2006) recommends refraining from vaccinating children with the MMR vaccine if they have moderate or severe acute illness; these guidelines may need to be revised to include less serious illness.

The presence of illness concurrent with the MMR vaccination and AD were not significantly associated when limiting the analysis to children 1 to 5 years old. This may be due to the small number of children in this subset, or it could be due to recall bias in that parents of older children are less accurate in their recollections. It is also possible that parents of the younger children are more accurate in their recollections, and there is no real effect.

In children, sulfation is the primary pathway for acetaminophen metabolism until age 10 to 12 years (Tucker, 2003). Children with autism usually have low levels of plasma sulfate which drives the sulfoconjugation reaction (Waring and Harris, 2005; Waring and Klovrza, 2000). Also, chronic inflammatory states, present in autistic children and probably in these affected children, since they have already had high doses of anti-inflammatory drugs, give raised levels of tumor necrosis factor alpha (TNF-α) which reduces the production of sulfate (Wilkinson and Waring, 2002). Sulfate is required for many biochemical pathways and is especially important in brain development/structure (Waring and Klovrza, 2000).

One pilot study reported a sulfation deficit in a small group of low-functioning children with AD which may cause them to process acetaminophen differently from control children (Alberti et al., 1999). This difference in processing acetaminophen could lead to increased production of N-acetyl-p-benzoquinone imine (NAPQI), a toxic by-product of acetaminophen metabolism. NAPQI could have interfered with the typical immune response to the MMR vaccination and precipitated AD in susceptible children. However, other models for the association of acetaminophen and AD are also possible, including direct neurotoxic effects of acetaminophen or NAPQI.

A potential concern in this study is that acetaminophen use after MMR vaccination was acting as a surrogate for sequelae to the MMR vaccination, i.e. it is really only the sequelae that are important. However, the use of acetaminophen after MMR vaccination produced a significant odds ratio (OR 8.23) after limiting the analysis to children who had post-vaccination sequelae. This is consistent with the idea that acetaminophen use after MMR vaccination is a risk factor for AD and not a surrogate measure for sequelae. The model would not converge when limited to children who did not have post-vaccination sequelae, and this analysis was not possible. Testing the interaction of acetaminophen use after MMR vaccination with the number of sequelae produced no significant results ($p > 0.05$).

One problem with this study is the reliance on self-report from the parents in reporting the exposures and the diagnosis of AD. Reliance on self-report can lead to misclassification bias. If the child's medical records were available, the problem of recording exposures would still exist since acetaminophen is available without a prescription and its use is not often recorded. Having medical records available would be beneficial to reducing AD misclassification since the diagnostic procedures could be verified. However, all of the parents of case children reported that their child was diagnosed by at least one medical professional.

Age in this study was limited to 1 to 18 years in an attempt to minimize recall bias in the parental responses. In a further attempt to minimize recall bias, a subgroup of children 1 to 5 years was also analyzed. However, it is possible that parents of children with AD may be more likely to remember and report acetaminophen use. It is also possible that children with AD are generally less healthy than their peers and are therefore more likely to be given acetaminophen.

Vaccination practices vary considerably throughout the world. Since this study was performed in the US, the results may not be generalizable to the rest of the world. The specific set of circumstances in this study may be unique to the US, and the results should be viewed with caution until replicated.

Since participants were recruited over the Internet and took the survey on a website, there is a possibility of ascertainment bias. Controls may not be representative of all non-cases in that they may have known a case or were searching the Internet for topics on autism. This difference is illustrated by the higher percentage of controls reporting fever after the MMR vaccination versus the percentage reported by the CDC (2006) for the general population (21% versus 5% to 15%). Both cases and controls may differ from the general population in that they have access to computers and are willing to take an online survey. Participants in this study most likely differed from the population in other ways as well, as this study was not a random sample.

There is a problem of missing data in this study as seen in the varying numbers of cases and controls in the analyses. Only surveys with responses to the question regarding acetaminophen use after MMR vaccination were included in this study; however, other questions suffered from non-response. The answers to questions on ibuprofen use were especially lacking, making the finding of no association of ibuprofen use with AD questionable. The survey is available from the authors by request.

This is the first case-control study to show a possible association of acetaminophen use with AD, and is consistent with our ecological study (Schultz et al., submitted). The findings may be coincidental. More research needs to be completed to confirm the results of this preliminary study.

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