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Autism 2007; 11; 301
DOI: 10.1177/1362361307078126

The online version of this article can be found at:
http://aut.sagepub.com/cgi/content/abstract/11/4/301

Published by:
SAGE
http://www.sagepublications.com

On behalf of:

The National Autistic Society

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Autistic Society
Vol 11(4) 301–310; 078126
1362-3613(200707)11:4

Developmental regression and autism reported to the Vaccine Adverse Event Reporting System

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ABSTRACT We report demographic and clinical characteristics of children reported to the US Vaccine Adverse Event Reporting System (VAERS) as having autism or another developmental disorder after vaccination. We completed 124 interviews with parents and reviewed medical records for 31 children whose records contained sufficient information to evaluate the child's developmental history. Medical record review indicated that 27 of 31 (87%) children had autism/ASD and 19 (61.3%) had evidence of developmental regression (loss of social, language, or motor skills). The proportion of VAERS cases of autism with regression was greater than that reported in population-based studies, based on the subset of VAERS cases with medical record confirmation. This difference may reflect preferential reporting to VAERS of autism with regression. In other respects, the children in this study appear to be similar to other children with autism. Further research might determine whether the pathogenesis of autism with developmental regression differs from that of autism without regression.

KEYWORDS *adverse event; autism; regression; vaccine*

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DOI: 10.1177/1362361307078126

Introduction

The onset of autism is sometimes marked by a regression of social, language, or motor skills, after a period of normal development. One-third to almost one-half of parents report regressive symptoms in their autistic children (Davidovitch et al., 2000; Kobayashi and Murata, 1998; Rapin, 1997; Tuchman and Rapin, 1997). It has been suggested that an environmental exposure, such as vaccine antigens or adjuvants (e.g. thimerosal), might trigger this regression (Blaxill et al., 2004; Wakefield et al., 1998). Accumulating evidence suggests that there is not a causal link between vaccines and autism (Akobeng and Thomas, 1999; Andrews et al., 2004; Fombonne and Chakrabarti, 2001; Heron et al., 2004; Hviid et al., 2003; Madsen et al., 2002; 2003; Makela et al., 2002; Smeeth et al., 2004; Taylor et al., 1999; 2002). The etiology of autism is likely to be multifactorial (Folstein, 1985; Institute of Medicine, 2004; Rapin, 1997), and differences in environmental exposures and genetic vulnerability to such exposures may influence the pathogenesis of autism in particular individuals (Folstein, 1985; Hornig et al., 2004). Using data from the Vaccine Adverse Event Reporting System (VAERS), we identified VAERS reports of autism and other developmental disorders and interviewed those VAERS reporters. We requested medical records pertaining to the child's developmental symptoms and asked clinical experts to verify the diagnosis of autism and the occurrence of regression. This analysis of VAERS data is intended to provide information for possible hypothesis generation on the subset of autistic children who, due to their reported regression, might be of the greatest interest for further study of any possible vaccine–autism association.

Methods

VAERS

VAERS is a national passive surveillance system that receives over 14,000 adverse event reports annually. Because of the limitations of passive surveillance systems such as VAERS (Chen et al., 1994; Ellenberg and Braun, 2002; Varricchio et al., 2004), it is usually not possible to make causal associations between vaccines and adverse events from VAERS reports. However, VAERS can help to generate hypotheses for confirmation with controlled study designs (CDC, 1999).

VAERS search strategy

Our search strategy has previously been summarized (Woo et al., 2004). Briefly, we searched VAERS for any report received between 1 July 1990

and 10 July 2001, with an adverse event description that suggested autism or a related developmental disorder, in individuals < 18 years old.

Survey instrument

After identifying VAERS reports of autism and other developmental disorders, we telephoned those parents and conducted structured interviews to characterize the children's symptoms after vaccination. The survey questionnaire addressed demographics, clinical characteristics, comorbidities, previous experience with vaccines, and family history. With permission, we also incorporated items from the Social Communication Questionnaire (SCQ, formerly the Autism Screening Questionnaire: Western Psychological Services, 2001), a validated (Berument et al., 1999) and abbreviated form of the Autism Diagnostic Interview–Revised (ADI–R: Lord et al., 1994), to address social, language, and motor development before and after the symptoms began. A score of 15 or greater suggests pervasive developmental delay, and a score of 22 or more suggests autism (Berument et al., 1999). The survey methods have been previously summarized (Woo et al., 2004).

Medical record review

Reporters who verbally agreed to have medical records requested from the treating physician were sent a consent form and a letter to explain the purpose of medical record review. Two autism experts (RL, a speech and language pathologist, and AWZ, a pediatric neurologist) reviewed medical records for pertinent information for the classification of autistic features and evaluation of medical histories of the cases, and to obtain, whenever possible, healthcare provider documentation of autism and the occurrence of regression.

Case definition and identification

Clinicians (RL and AZ) who are experienced in the diagnosis of autism independently classified the cases as definite autism, suspected autism, or not autism. When available, results of the Autism Diagnostic Interview were also reviewed. Cases were then independently classified as definite regression, suspected regression, or not regression, based on documentation of a decline or loss of social, language, or motor skills (e.g. interactive play, number of words spoken, and ability to feed self). Disagreements about the classification of autism and regression were resolved by discussion and consensus between the two autism experts. For both autism and regression, we assessed the concordance of the experts' review, by calculating agreement (McNemar, 1947).

Data analysis

The data were summarized with descriptive statistics. For both autism and regression, we assessed the concordance of expert review of medical records and parental reports during interviews, by calculating agreement (McNemar, 1947).

Contributing factors

Records were assessed for alternative explanations for, or contributing factors to, each child's developmental delay, such as known genetic/chromosomal causes (e.g. fragile X syndrome), perinatal infections, accelerated brain growth (Courchesne et al., 2003), and advanced parental age (Bertrand et al., 2001; Croen et al., 2002; Glasson et al., 2004).

Institutional review board approval

The FDA's Research Involving Human Subjects Committee reviewed and approved all study procedures and documents.

Results

Subject identification

Subject identification is summarized in Figure 1. We identified 351 VAERS reports from 1 July 1990 to 10 July 2001 with COSTARTs or symptom descriptions that suggested autism or a related disorder. Two hundred reporters could not be contacted, and 27 refused to participate (in one case because the child had never had any autistic symptoms). The study included 124 reporters who were interviewed. Medical records for 43 children were received and ranged widely in their quality and volume. Some contained only an infant growth chart and immunization records, while others contained detailed neurodevelopmental evaluations and other relevant records.

Autism and regression

Table 1 summarizes demographic and clinical characteristics of the children with autism reported to VAERS. Regarding autism, the expert reviewers initially disagreed about one case (3.2%) out of the 31 whose medical records were reviewed. By consensus they confirmed 27 (87.1%) cases of autism (26 definite and one suspected). The medical records largely corroborated parental descriptions of regression of social, language, or motor skills. Regarding regression, the expert reviewers initially disagreed in 10 (32.3%) of the 31 cases, but they then determined by consensus that 19 (61.3%) children had developmental regression (10 definite and nine suspected), including two children who the experts did not think had autism. In 26

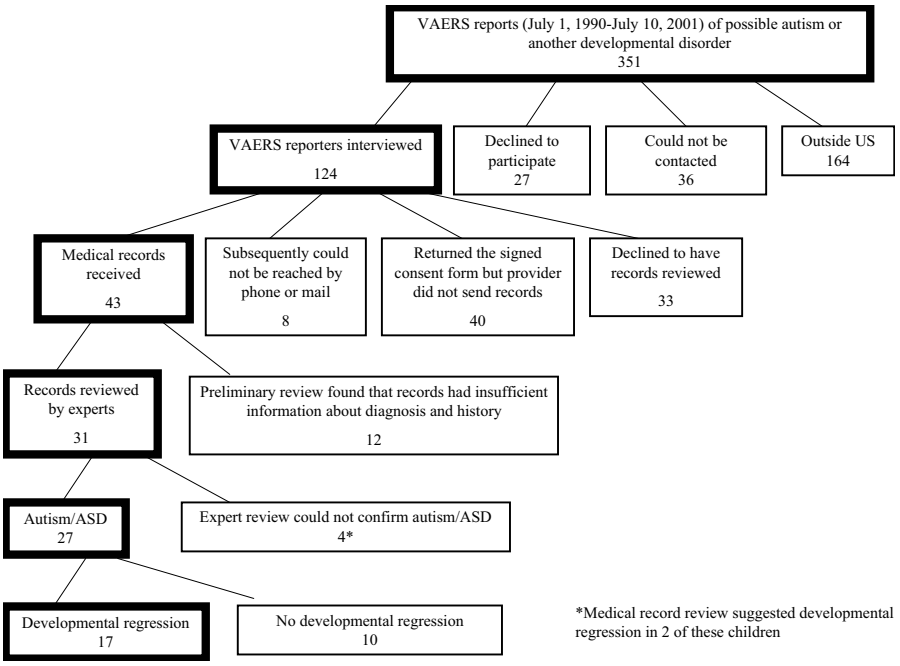

Figure 1 **Subject identification**

(83.9%) of cases for which records were reviewed, the experts' assessment and parental reports agreed on the diagnosis of autism. In 24 (77.4%) cases, expert review and parental reports agreed on the occurrence of regression.

Possible alternative explanations and contributing factors

Alternative explanations for, and contributing factors to, the patient's autism were common (Table 2); no clear pattern or cluster of events (such as encephalopathy) was observed that would suggest a possible mechanism or explanation for neurological injury. Similarly, comorbidities, such as seizures and gastrointestinal symptoms, were common (Table 2), but their temporal relationship with vaccination and autistic symptoms varied and thus did not provide any clues about possible etiologic factors. Eight (25.8%) records mentioned immunoglobulin assays or other tests of immunity in the affected child; the results provided for two were normal, and results for the other six were not provided. Four medical records (12.9%) described macrocephaly, but it was not always clear whether this abnormality was due to the accelerated brain growth that is typical in autism (Courchesne et al., 2003). Three records (9.7%) suggested a possible mitochondrial disorder. No genetic or chromosomal abnormalities were

Table 1 **Parental interviews and medical record review for autism reports to VAERS**

	Parental interview only n = 93[a]	*Parental interview and medical record review n = 31*
Demographics		
Male sex	77 (82.8%)	29 (93.6%)
Age at onset, months (median, 25th %ile, 75th %ile)	15.5 (12.3, 18.3)	15.3 (12.3, 17.4)
Interval between vaccination and symptoms, days (median, 25th %ile, 75th %ile)	30 (8, 60)	30 (8, 120)
Parental interviews		
Parent reports diagnosis of autism	67 (72.0%)	26 (83.9%)
Parent reports regression[b]	81 (87.1%)	20 (64.5%)
SCQ score ≥ 22[c]	53 (57.0%)	23 (74.2%)
SCQ score ≥ 15[c]	82 (88.2%)	29 (93.5%)
Child's chronological age, years (median, 25th %ile, 75th %ile)	6.0 (4.9, 9.5)	6.2 (4.5, 9.2)
Child's functional age, years (median, 25th %ile, 75th %ile)	3.0 (2.0, 5.0)	2.5 (2.0, 4.0)
Words spoken before event (median, 25th %ile, 75th %ile)	12 (5, 40)	8 (3, 12)
Words spoken after event (median, 25th %ile, 75th %ile)	0 (0, 1)	0 (0, 0)
Expert review of medical records		
Definite or suspected autism	not applicable	27 (87.1%)
Definite or suspected regression	not applicable	19 (61.3%)

[a] Age at onset was available for only 86 of these children.
[b] Parent reports that development was normal or high before the event and low afterwards.
[c] SCQ scores are derived from parental interview responses: see text.

identified in the submitted medical records. Three (9.7%) medical records mentioned tests for heavy metal levels; the results provided for two were normal, and the results of one included a hair lead level of 1.5 μg/g (reference range in that laboratory is < 1.0 μg/g) and a normal hair mercury level. One record (3.2%) mentioned maternal exposure to lead during pregnancy, but no details were provided.

Parental interviews

Responses to questions during parental interviews are included in Table 1. The functional age was noted to be lower than the chronological age, the numbers of words that the child spoke was larger before than after the onset of symptoms, and parents reported that development before the event began had been normal or high, but that it had been low ever since.

Table 2 **Comorbidities and family history**

	Parental interview only n = 93	*Parental interview and medical record review n = 31*	
		Interview	*Record review*
Gastrointestinal symptoms/signs	69 (74.2%)	18 (58.1%)	18 (58.1%)
Seizure disorders	17 (18.3%)	7 (23.6%)	6 (19.6%)
Obstetrical/perinatal complications:[a]	38 (40.9%)	12 (38.7%)	15 (48.4%)
High blood pressure	3 (3.2%)	0	1 (3.2%)
Gestational diabetes	2 (2.2%)	1 (3.2%)	1 (3.2%)
Pre- or intrapartum infection	3 (3.2%)	0	0
Neonatal complications[b]	21 (22.6%)	9 (29.0%)	7 (22.6%)
Other[c]	16 (17.2%)	3 (9.7%)	13 (41.9%)
Family history of developmental disorder or psychiatric illness:[a]	20 (21.5%)	4 (12.9%)	10 (32.3%)
Autism	4 (4.3%)	0	2 (6.5%)
Schizophrenia	1 (1.1%)	0	0
Mental retardation	2 (2.2%)	0	0
Learning disorder	16 (17.2%)	4 (12.9%)	8 (25.8%)

[a] Symptoms in each category are not mutually exclusive.
[b] For example, apnea, hypoglycemia, atrial flutter, or fever.
[c] For example, hyperemesis gravidarum, uterine bleeding during first trimester, oligohydramnios in child's twin, or group B Streptococcus infection.

Please also see text regarding reported mitochondrial disorders, macrocephaly, and metal exposure in the 31 children for whom both interview data and medical records were available.

Table 2 summarizes parental report of comorbidities, perinatal history, and family history. According to the 124 reporter interviews, the median maternal age at the time of birth of the child for whom a VAERS report was submitted was 31.2 years. No preterm deliveries (< 37 weeks) were reported, although 18 (14.5%) of the pregnancies were post-dates (> 42 weeks).

Discussion

As in other settings (Bertrand et al., 2001; Chakrabarti and Fombonne, 2001; Rapin, 1997; Tuchman and Rapin, 1997), the vast majority of the VAERS autism children were male, most were 12 to 18 months old when their symptoms were first noticed, and they demonstrated delays or impairments of verbal and non-verbal communication, social skills, attention, and learning. Stereotyped, repetitive movements, and unusual interests were also common among the VAERS autism children. Our study of VAERS autism cases revealed a higher proportion of regression in social, language, behavioral,

and motor skills than described in population-based studies. Other than this higher proportion with regression, these children appear to be similar to other children with autism and other developmental disorders, and the role of preferential reporting must be considered. The parents of children whose autism involved regression may have been more likely to report to VAERS because of hypotheses about an environmental trigger and because of the temporal association of their children's symptoms with vaccination. Furthermore, because of the low proportion of respondent participation, especially for medical record submission, our results must be interpreted carefully. The low response rate in our study and the incomplete information in some medical records may have limited our ability to identify any specific factor that might contribute to the etiology of autism and regression. Nevertheless, our data in part fill an information gap.

We previously described the risk perception of parents who reported autism to VAERS (Woo et al., 2004), but in the present study our objective was to search for clinical information that might help to provide clues that could, through subsequent investigations, lead to explanations about developmental regression. The Immunization Safety Review Committee of the Institute of Medicine (IOM) has rejected a causal relationship between vaccines and autism (Institute of Medicine, 2004). However, the Committee repeated its previous recommendation that studies be conducted to identify risk factors for autism. Although VAERS is not designed to determine causal relationships between vaccines and adverse events, its data can be used to generate hypotheses about possible biological mechanisms for the development of autism. This review of autism cases reported to VAERS did not clearly identify additional clues about the etiology of autism or regression after vaccination, related to heavy metal metabolism, immunity, or genetic factors.

Acknowledgements

We thank Dr Dale R. Burwen, Dr Susan L. Connors, Dr Susan Ellenberg, and Dr Frederick Varricchio for critical review of the manuscript. We thank Battelle Center for Public Health Research for assistance with interviews, correspondence, and data entry. We also greatly appreciate the efforts of the VAERS Working Group for their dedication to the maintenance of VAERS. The members of the VAERS Working Group include: Marthe Bryant-Genevier, Dale R. Burwen, Soju Chang, Azra Dobardzic, Hector Izurieta, Ann W. McMahon, Phil Perucci, and Lise Stevens (Food and Drug Administration); Scott Campbell, Penina Haber, John Iskander, Elaine Miller, and Gina T. Mootrey (Centers for Disease Control and Prevention); and Vito Caserta (Health Resources and Services Administration). Funding in part was provided by the National Vaccine Program Office.

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