

# PEDIATRIC NEUROLOGY BRIEFS

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### SEIZURE DISORDERS

#### **RISK OF SEIZURES FOLLOWING DTP AND MMR VACCINES**

The risk of a first seizure, subsequent seizures, and neurodevelopmental disability following the administration of diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine and measles, mumps, and rubella (MMR) vaccine was studied by a retrospective review of children's medical records at four health maintenance organizations, including University of Washington, Seattle; and Kaiser Permanente Groups in OR and CA, members of the CDC & P Vaccine Safety Datalink Project. Data were collected from more than 600,000 enrolled children (under age 7 years) between 1991 and 1993. Seizures were identified by automated data systems on hospitalizations and clinic visits and by random-sampling of medical records. Simple febrile seizures were defined as short and generalized, and complex febrile seizures occurred more than once in 24 hours, lasted at least 12 minutes or were focal. Nonfebrile seizures due to prior infection or trauma were excluded. The background rate of febrile seizures during the first two years of life was used to calculate the risk attributable to immunization. Following 340,386 DTP and 137,457 MMR vaccinations, 2281 first seizures were identified using automated data, and 716 first seizures from random sampling and chart review of 1094 children. First seizures were febrile in 487 (460 simple, 27 complex), nonfebrile in 137, infantile spasms or neonatal in 36, and other causes in 56. Febrile seizures occurred within 30 days after DTP and MMR vaccines in 42 (5 on the same day as DTP) and 32, respectively. Febrile seizures were recorded in the absence of vaccination in 521 children. Nonfebrile seizures occurred within 30 days after DTP and MMR vaccines in 10 and 3 children, respectively.

DTP was associated with a significantly increased risk of febrile seizures on the day of vaccination (relative risk, 5.70; 95% confidence interval, 1.98-16.42). MMR was also associated with increased risk of febrile seizures 8 to 14 days after vaccination (RR 5.7; 95% CI, 1.44-5.55). The estimated numbers of febrile seizures attributable to DTP and MMR vaccination were 6 to 9 and 25 to 34 per 100,000 children, respectively. Of the children with febrile seizures not related to vaccination, 5 percent had developed epilepsy at two year follow-up. Febrile

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seizures associated with vaccination did not carry a higher risk of subsequent epilepsy or neurodevelopmental disabilities (ADHD, learning disorders, retardation, infantile autism, other emotional and behavior disorders) than non-vaccine related febrile seizures. (Barlow WE, Davis RL, Glasser JW et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med August 30, 2001;345:656-661). (Reprints: Dr Robert L Davis, Center for Health Studies, Group Health Cooperative, 1730 Minor Ave, Suite 1600, Seattle, WA 98101).

**COMMENT.** The Vaccine Safety Datalink project, initiated by the Centers for Disease Control and Prevention in 1991, is a large population-based study of adverse events associated with childhood immunizations. Use of the automated system allows a more rapid assessment of risks and shows good concordance with analyses of cases by record review. In the present study of whole-cell pertussis in DTP vaccine and the MMR vaccine, the risk of febrile seizures is significantly increased following either vaccine.

Febrile seizures carry an increased risk of unprovoked seizures and epilepsy. In the present study, the risk in vaccine-related seizures is not significant (10 cases after DTP, 3 with MMR); the risk is 5 percent for febrile seizures not induced by vaccination, at two year follow-up, and similar to that reported in previous research (Millichap, JG. Febrile Convulsions, New York, Macmillan, 1968; Berg AT, Shinnar S, Neurology 1996;47:562-568). Risk factors for nonfebrile seizures include complex febrile seizures, neurodevelopmental abnormalities, family history of epilepsy, and recurrent febrile seizures (Nelson KB, Ellenberg JH. Eds. Febrile Seizures. New York, Raven Press, 1981). The majority of vaccine-related febrile seizures in the CDC study were simple in type, which explains the low incidence of subsequent epilepsy. Patients with complex febrile seizures have a higher risk of epilepsy than those with simple febrile seizures (10-20% vs 2-3%, respectively). Of children with no febrile seizures, only 0.4% develop epilepsy by age 10 years (Verity CM, Golding J. BMJ 1991;303:1373-6).

Behavioral and neurodevelopmental disorders have been reported in children with a history of febrile seizures. Studies of twins discordant for febrile seizures offer the most convincing data suggesting cause and effect. (Schiotz-Christensen E, Bruhn P. Dev Med Child Neurol 1973;15:565-575). Whole-cell pertussis vaccine, in common use worldwide, has been replaced by acellular pertussis vaccine in the United States, with less potential for adverse events. The benefits of vaccination in general outweigh the increased risk of febrile seizures and related side effects. Precautions for pertussis immunization and reasons for avoidance, interruption, or deferment are listed in the AAP Red Book, 2000;446-448.

**Generalized epilepsy with FS plus (GEFS+).** Two novel disease mutations of a subunit of the sodium channel are reported in Japanese patients with febrile seizures associated with afebrile partial seizures (Sugawara T, Mazaki-Miyazaki E, Ito M et al. Neurology 2001;57:703-705). Previous reports of a clinical subset of FS with generalized epilepsy (GEFS+) have found loci on chromosomes 19q and 2q. An understanding of the molecular pathology of FS associated with afebrile seizures will help to elucidate risks of epilepsy associated with febrile seizures and vaccination.