

Acute Encephalopathy Followed by Permanent Brain Injury or Death Associated With Further Attenuated Measles Vaccines: A Review of Claims Submitted to the National Vaccine Injury Compensation Program

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ABSTRACT. *Objective.* To determine if there is evidence for a causal relationship between acute encephalopathy followed by permanent brain injury or death associated with the administration of further attenuated measles vaccines (Attenuvax or Lirugen, Hoechst Marion Roussel, Kansas City, MO), mumps vaccine (Mumpsvax, Merck and Co, Inc, West Point, PA), or rubella vaccines (Meruvax or Meruvax II, Merck and Co, Inc, West Point, PA), combined measles and rubella vaccine (M-R-Vax or M-R-Vax II, Merck and Co, Inc, West Point, PA), or combined measles, mumps, and rubella vaccine (M-M-R or M-M-R II, Merck and Co, Inc, West Point, PA), the lead author reviewed claims submitted to the National Vaccine Injury Compensation Program.

Methods. The medical records of children who met the inclusion criteria of receiving the first dose of these vaccines between 1970 and 1993 and who developed such an encephalopathy with no determined cause within 15 days were identified and analyzed.

Results. A total of 48 children, ages 10 to 49 months, met the inclusion criteria after receiving measles vaccine, alone or in combination. Eight children died, and the remainder had mental regression and retardation, chronic seizures, motor and sensory deficits, and movement disorders. The onset of neurologic signs or symptoms occurred with a nonrandom, statistically significant distribution of cases on days 8 and 9. No cases were identified after the administration of monovalent mumps or rubella vaccine.

Conclusions. This clustering suggests that a causal relationship between measles vaccine and encephalopathy may exist as a rare complication of measles immunization. *Pediatrics* 1998;101:383-387; *measles vaccine, encephalopathy, encephalitis.*

ABBREVIATIONS. MR, measles-rubella vaccine; MMR, measles-mumps-rubella vaccine; DTP, diphtheria, tetanus, pertussis vaccine; Hib, *Haemophilus influenzae* type b vaccine; OPV, oral poliovirus vaccine; CSF, cerebrospinal fluid.

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Live attenuated measles vaccines used in the United States have almost eliminated natural measles and its complications.¹ The Edmonston B strain of live attenuated measles virus vaccine induced fever >103°F in approximately one third and a measles-like rash in approximately one half of vaccine recipients.² This vaccine, first licensed for general use in the United States on March 21, 1963, was simultaneously administered with 0.02 mL/kg of human immunoglobulin that greatly reduced the occurrence of fever and rash. Further, more attenuated, Edmonston-Enders measles vaccines were developed to eliminate the use of immunoglobulin. The Schwarz strain (Lirugen) was licensed on February 2, 1965, and used until 1976. Edmonston-Enders strain (Attenuvax), licensed on November 26, 1968, was combined with rubella vaccine (MR) or mumps and rubella (MMR) and licensed on April 22, 1971. MMR soon became the preferred immunization, and by 1976, Attenuvax became the only measles strain distributed in the United States. On September 15, 1978, United States licensure of RA27/3 strain of MR replaced the HPV-77 (duck embryo) strain licensed on June 9, 1969, and II was added to the trade names.

Postinfectious encephalopathy complicates approximately 1 in 1000 cases of natural measles and results in a mortality rate of 10% to 20% and permanent central nervous system impairment in the majority of survivors.³⁻⁶ Encephalopathy, in this report, is defined as any significant acquired abnormality of, injury to, or impairment of function of the brain, with or without an inflammatory response (ie, encephalitis, encephalomyelitis). The onset of encephalopathy usually occurs 2 to 7 days after the rash. Pleocytosis is reported in approximately 20% of these patients. The cause of this acute monophasic encephalopathy that occurs in the absence of a detectable virus in the brain is obscure, but may be suggestive of an autoimmune encephalopathy. This disease is distinct from progressive subacute sclerosing panencephalitis or subacute inclusion-body encephalitis in immunodeficient patients caused by a persistent measles virus infection.^{7,8}

Case reports and reviews suggest that similar neurologic complications can, less frequently, follow the administration of live attenuated measles vaccine.⁹⁻¹¹ In 1973, Landrigan and Witte¹¹ reviewed 84 patients with the onset of neurologic disorders within 30 days after a live measles vaccination who were reported to the Centers for Disease Control and Prevention from 1963 to 1971. Encephalopathy (used interchangeably

with encephalitis) of undetermined cause occurred 1 to 25 days after vaccination in 59 patients, and of these, 45 patients had an onset 6 to 15 days after vaccination. Long-term follow-up of 50 of the 59 patients revealed that 5 died, 19 had persistent encephalopathy, and 26 had recovered fully. In a study of the incidence of encephalitis in Olmsted County, Minnesota, from 1950 to 1981 by Beghi et al,¹² 78% of the patients recovered completely.

In the National Childhood Encephalopathy Study of the United Kingdom from July 1, 1976 to June 30, 1979, Alderslade et al¹³ reported convulsions or acute encephalopathy, without separating the two conditions, in 17 children 7 to 14 days after receiving the Schwarz strain measles vaccine, and in 10 unvaccinated age-matched controls from the local community. This study, designed to assess serious neurologic disorders associated with whole-cell pertussis vaccine, reported the onset of encephalopathy <7 days after the administration of whole-cell pertussis.

The purpose of this study of claims submitted to the National Vaccine Injury Compensation Program is to determine whether or not there is evidence for a causal relationship between the first dose of a currently used attenuated measles vaccine, MR, MMR, mumps, or rubella vaccine and encephalopathy of undetermined cause with permanent brain injury or death that occurred within 15 days after administration.

STATUTORY FRAMEWORK

The National Childhood Vaccine Injury Act of 1986 established the compensation program, a federal no-fault system that became effective on October 1, 1988, to provide compensation for individuals who were injured or who died as a result of specified immunizations.¹⁴ Claims of encephalopathy, seizure disorder, or death after the administration of covered vaccines, including measles, mumps, or rubella, can be submitted to the program and awarded compensation, if the condition meets certain medical and legal qualifications. For an individual who received a measles, mumps, or rubella vaccine, the act grants, in the Vaccine Injury Table, the presumption of vaccine causation if the first manifestation of encephalopathy occurs, in the absence of an alternate cause, 15 days or less after receiving any of these vaccines. The injury or its residual effects, except when death occurs, must persist for >6 months. The standard of proof is a preponderance of the medical evidence (ie, >50%, or more likely than not). In addition, a vaccine cause may be demonstrated in the absence of a Vaccine Table Injury, but legally, this is a more difficult process for the person seeking compensation. Effective March 10, 1995, the program changed the time period of a Vaccine Table Injury for these vaccines and the onset of encephalopathy from <15 days to 5 to 15 days.¹⁵

In 1994, an Institute of Medicine Committee published a scientific review of clinical studies and case series and reports of encephalopathy after the administration of measles, MR, MMR, and mumps vaccine.⁹ Their review identified no conclusive evidence of the occurrence of encephalopathy or encephalitis after the administration of measles or mumps vaccine. Nevertheless, the Institute of Medicine Committee acknowl-

edged biologic plausibility that measles vaccine might cause encephalopathy. The lack of controlled studies that distinguish background rates of encephalopathy of undetermined cause in unvaccinated populations makes a determination of causation difficult.

METHODS

The medical records and affidavits in each petition are reviewed by physicians in the compensation program to determine, if possible, the cause of the injury and to classify the findings. The program's finding as to the onset of neurologic signs or symptoms is based only on the medical records. The diagnosis in each case is based on the preponderance of the medical evidence and the assessments of the treating physicians. When deemed necessary, a medical expert is obtained to review the case and provide an expert opinion. All of the cases of encephalopathy discussed in this article have been reviewed in a consistent manner by the first author.

Children with appropriate development who acquired an acute encephalopathy of undetermined cause within 15 days after the administration of the first dose of measles, MR, MMR, mumps, or rubella vaccine between April 1970 and March 1993 followed by chronic encephalopathy or death were selected for further analysis. The neurologic criteria used for the diagnosis of acute encephalopathy of undetermined cause were an abrupt onset of neurologic symptoms and/or signs with significant brain impairment including behavior changes with a depressed level of consciousness, ataxia, or seizures. Children selected for this study had an acute encephalopathic illness followed by chronic encephalopathy including mental retardation, seizure disorders, movement disorders, or motor or sensory disorders.

Cases of encephalopathy were excluded if an infectious, toxic, traumatic, or metabolic cause or a recent exposure to natural measles, mumps, or rubella was identified or full recovery occurred within 6 months. Seizures with mental dysfunction attributed to the postnatal state or medication were not considered to be encephalopathy.

All children at the time of the vaccination were considered by the authors to be susceptible to the vaccines administered and >95% would be expected to develop an immune response to the vaccines. The evaluation of these children reflects the standards and technical advancements for diagnoses at the time of the injury. In a few instances, attempts to isolate virus from cerebral tissue and cerebrospinal fluid were unsuccessful. Viral isolation and antibody studies for arboviruses, enteroviruses, and herpesvirus were negative on all children evaluated.

Identified patients were categorized with the variables of sex, vaccine or vaccines administered, age at vaccination, postvaccination day of onset, neurologic symptom at onset, level of consciousness or behavior changes during the day of onset, fever, measles-like rash, cerebrospinal fluid analysis, developmental regression during or after the acute illness, hospitalization, antibody studies, and manifestations of permanent brain injury or death.

RESULTS

A total of 403 claims of encephalopathy and/or seizure disorder after measles, MR, MMR, mumps, or rubella vaccination were identified during this 23-year period. Of these claims, 48 (25 males and 23 females) met the inclusion criteria and acquired an acute encephalopathy of undetermined cause 2 to 15 days after receiving measles vaccine, MR, or MMR. This acute encephalopathy was followed by permanent brain impairment or death. The patients ranged in age from 10 months to 49 months, with a median age of 15 months and a mean age of 17.5 months. No case of encephalopathy of undetermined cause within 15 days after the administration of monovalent mumps or rubella vaccine was identified.

Either Attenuvax or Lirugen was administered to 4 children between 1970 and 1974, and Attenuvax was administered to 4 children between 1977 and 1982. One child received MR, and 30 children received MMR. Of the remaining 9 children, 2 received MMR and diph-

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theria, tetanus, pertussis vaccine (DTP), 2 received MMR and *Haemophilus influenzae* type b vaccine (Hib), 4 received MMR, DTP, and oral poliovirus vaccine (OPV), and 1 received MMR, DTP, OPV, and Hib.

The onset of these 48 cases of encephalopathy (Fig 1) occurred 2 to 15 days after the administration of a measles-containing vaccine. All patients were apparently well during the first 48 hours after the vaccination (postimmunization days 0 and 1). The clustering and peak onset of encephalopathy occurred in 17 patients on days 8 and 9. Of the 12 cases of encephalopathy that occurred within 7 days after vaccination, 10 received only MMR; 1 with an onset on day 4 received MMR and Hib; and 1 with an onset on day 5 received MMR and DTP.

The clinical features of acute and chronic encephalopathy or death in these 48 patients (Table 1) were classified into three groups based on the initial finding of ataxia in 6, behavior changes in 8, and seizures in 34. The onset of neurologic findings varied in severity from ataxia or behavior changes to prolonged seizures or coma. Fever preceded the onset of acute encephalopathy by several hours to several days in 43 of 48 children. A measles-like rash with a postvaccination onset from day 6 to 15 occurred in 13 children.

All children with acute ataxia had significant behavior changes, and 3 of the 6 were hospitalized. Neurologic sequelae in the ataxia group included mental retardation in 3, seizure disorder in 1, chronic ataxia in 4, and sensorineural hearing loss in 1.

A case example of this group is a normal 16-month-old female who received MMR, and 9 days later, she had a fever, a measles-like rash, and ataxia. Neurologic examinations revealed unsteadiness and truncal titubation, nystagmus, dysmetria, developmental regression, and pleocytosis with 41 monocytes, and a normal brain scan with magnetic resonance imaging. She was diagnosed as having brainstem encephalitis. At age 10 years, she had global developmental delay and cerebellar dysfunction.

The 8 children with initial behavior changes rapidly progressed to coma. Two died during the acute illness with autopsy findings of massive cerebral

edema and herniation. Of the 6 survivors, 6 had mental retardation, 5 spastic paresis, 1 seizure disorder, 1 choreoathetosis, and 1 died 6 years after the acute illness.

A case example of this group is a normal 29-month-old male who received MMR and Hib, and 14 days later, he developed fever, emesis, and progressive lethargy. The following day, he was hospitalized in coma with pleocytosis (246 monocytes, 54 lymphocytes), an elevated cerebrospinal fluid (CSF) protein (49), negative CSF bacterial and viral cultures, and an electroencephalogram (EEG) with diffuse cerebral slowing. He became rigid and opisthotonic. Magnetic resonance imaging of the brain revealed leukodystrophy. At age 5 years, he had hyperactivity and aggressive behavior.

In the 34 children with an onset of generalized or focal seizures, coma and behavior changes could not be attributed to a postictal state or medication. These seizures, associated with fever in 32 and a measles-like rash in 9, rapidly progressed to coma in 29 and depressed or changed consciousness in 5. Two apparently normal healthy children received MMR vaccine and died 2 and 12 days later. Autopsy findings revealed cerebral edema and uncus gyral herniation in one, and viral encephalitis with hemorrhagic infarctions of the thalamus and pons in the other. All survivors had chronic encephalopathy with mental retardation in 31, seizure disorder in 23, and spastic paresis in 10. Three deaths occurred 3 months to 4 years later.

A case example of this group is a normal 16-month-old female who received measles vaccine, and 7 days later, she developed a fever and a measles-like rash. Ten days after the vaccination, she was hospitalized with status epilepticus, a temperature of 106°F, and a normal CSF analysis. The following day, she had intermittent seizures on anticonvulsant therapy, coma, and left hemiparesis. An EEG showed totally disorganized activity, epileptiform discharges, and right hemisphere suppression. At age 10 years, she had spastic left hemiparesis and cognitive difficulties.

CSF analyses performed on 40 of the 48 children were abnormal in 16. Pleocytosis, mainly mononu-

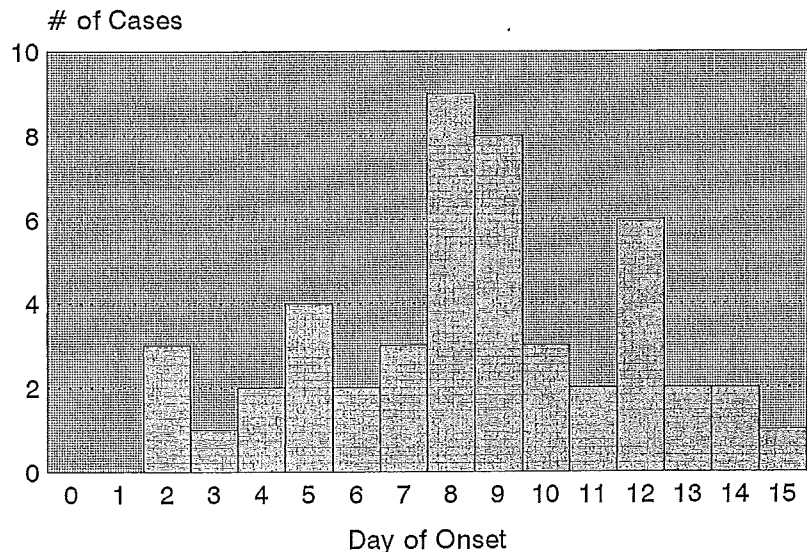


Fig 1. Onset of encephalopathy by day after the administration of the first dose of MMR, MR, or further attenuated measles vaccine in 48 children (1970-1993).

TABLE 1. Clinical Findings of Acute Encephalopathy Among 48 Patients 2-15 Days After the First Dose of a Further Attenuated Measles Vaccine, MR, or MMR, 1970-1993, and Sequelae

Clinical Onset	No.	Acute Illness	No.	Neurologic Sequelae	No.
Ataxia	6	Ataxia	6	Ataxia (chronic)	4
Irritability	6	Behavior changes	6	Mental retardation	3
Fever	5	Mental regression	4	Seizure disorder	1
Measles-like rash	3	Hospitalization	3	Hearing loss	1
Behavior changes	8				
Lethargy	3	Coma	8	Mental retardation	6
Irritability	2	Mental regression	5	Spastic paresis	5
Confusion	2	Hospitalization	6	Seizure disorder	1
Coma	1	Death	2	Choreoathetosis	1
Fever	6			Death (later)	1
Measles-like rash	1				
Seizures	34				
Status epilepticus	17	Coma	29	Mental retardation	31
Generalized	14	Behavior changes	5	Seizure disorder	23
Focal	3	Mental regression	31	Spastic paresis	10
Fever	32	Hospitalization	33	Death (later)	3
Measles-like rash	9	Death	2		

clear cells, ranged from 7 to 246 cells in 11 patients, with an elevated protein of 49 mg to 101 mg in 4 of these 11. Four patients had only an elevated CSF protein of 117 to 172 mg/dL and 1 had an elevated CSF pressure of 320 mm H₂O without further CSF analyses recorded.

The 48 patients (Table 2) are divided into three time periods based on an onset day of 1 to 5, 6 to 10, and 11 to 15. The onset of ataxia, behavior changes, seizures, and CSF pleocytosis occurred in each time period, with approximately one half of the cases in the 6 to 10 day time period. The acute illness was associated with fever in all but 5 patients; 3 of the afebrile children were in the 1 to 5 day time period.

The distribution of encephalopathy by month of onset (Fig 2) is random throughout the year with a variation of 10 to 13 cases by season. By year of onset, the number of cases ranged from 0 to 4 each year with a total of 15 in the 1970s, 1 to 5 with a total of 21 in the 1980s, and 1 to 6 with a total of 12 in the 1990s with a peak in 1989 and 1990 and no trend in the pattern throughout the years. The medical evaluations reflected the standards of each time period. Pre vaccination clinical records revealed no evidence of hypersensitivity.

Statistical Analysis

A statistical analysis was performed on the distribution of the 48 cases that met the inclusion criteria. A random distribution would show the onset of 3.0 cases/day (48 ÷ 16). The denominator of 16 is used because the inclusion criterion within 15 days includes 16 periods of 24 hours when the day of immunization is counted as day 0. A comparison of the observed number to the expected number per day was performed based on the use of a standardized

morbidity ratio. The distribution was nonrandom with clustering and 2 statistically significant increases (0.01 < P < .05) of 9 and 8 cases on postvaccination days 8 and 9, respectively.¹⁶ Our analysis found no significant difference between the onset of encephalopathy and age or sex. In the absence of any obvious bias and confounding, this finding is evidence for a causal relationship between further attenuated measles vaccine, alone or in combination, and acute encephalopathy of undetermined cause followed by permanent brain impairment or death.

DISCUSSION

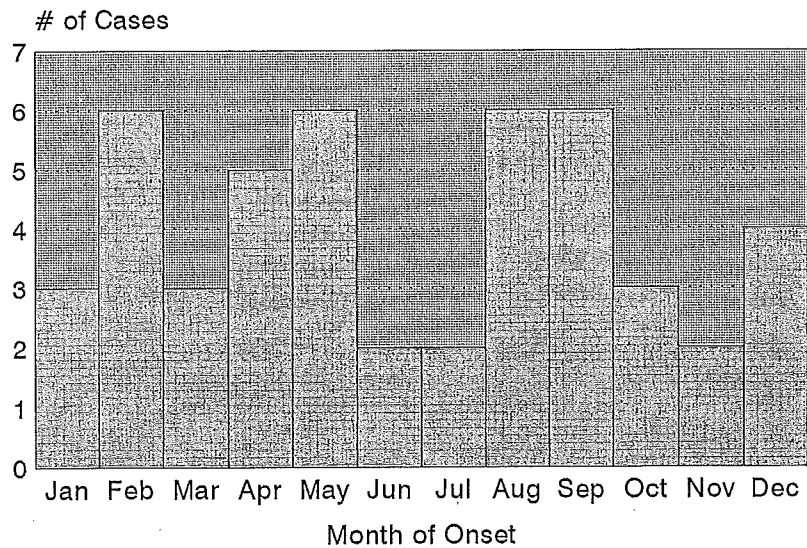
Manifestations of acute encephalopathy including loss of consciousness, ataxia, seizures, and pleocytosis among these 48 children is similar to the clinical features of acute encephalopathy described after natural measles and other live measles vaccines.^{1,2,4,8,10} The earlier onset of these cases of encephalopathy after the injection of live attenuated measles vaccine as compared with the onset after natural respiratory exposure to wild-type measles virus may be related to the route of entry, as is the earlier onset of measles-like symptoms and immune responses.¹⁷ Whether the onset of encephalopathy within 5 days after a measles vaccination can be caused by vaccine virus replication and immune responses is not clear.

Encephalopathy after natural measles is known to occur in young children, and in some, there is full recovery. Among children in England and Wales, Miller et al⁶ reported 389 cases of encephalitis after natural measles with 11% of these cases at age 1 to 2 years and 13% at 3 to 4 years. It is biologically plausible that encephalopathy with variable outcomes could occur after measles vaccine administered to children of the same age.

TABLE 2. Clinical Findings in 48 Patients Through Postvaccination Day 15 by Type of Neurologic Onset in 5-Day Period Groups

Onset Days	Total	Ataxia	Behavior Changes	Seizures	Fever	Rash	CSF Pleocytosis
1-5	10	1	2	7	7	0	3
6-10	25	4	4	17	24	10	5
11-15	13	1	2	10	12	3	3
	48						

Fig 2. Onset of encephalopathy by month after the administration of the first dose of MMR, MR, or further attenuated measles vaccine in 48 children (1970–1993).



A comparison of these cases to claims seeking compensation could be biased, but there is no evidence for bias in the recording of the onset of acute encephalopathy in the medical records or the selection of cases analyzed. Study of this issue is hampered by a lack of background encephalopathic rates in unvaccinated children. A review of similar cases reported to other systems could be helpful.

Claims with an onset of acute encephalopathy of undetermined cause within 15 days after a measles, MR, MMR, mumps, or rubella vaccination between 1970 and 1993 followed by permanent brain injury or death have an equal likelihood of being recommended for compensation by the program physicians regardless of whether the injury began on day 0 or day 15. If the null hypothesis is true and the measles, mumps, or rubella vaccine has no causal relationship to the acute encephalopathy, the number of cases with an onset of neurologic findings of encephalopathy each day during this period would be expected to have a random distribution with essentially equal numbers of cases on each day. Our results of a statistically significant cluster on days 8 and 9 after measles immunization indicates this may be an effect of measles vaccine, MR, and MMR.

From 1970 to 1993 in the United States, approximately 75 000 000 children received measles vaccine by age 4 years based on 83 000 000 births and an immunization rate of 90%. The 48 cases of encephalopathy probably represent underreporting to this passive system, which does not require individuals to file for compensation and requires medical documentation. However, given the generous compensation offered in this program, it is reasonable to conclude that most serious cases temporally related to a vaccination have been captured. In the absence of a specific test to determine vaccine causation, these 48 cases may include some nonvaccine cases representing background rates. Nevertheless, with a denominator of 75 000 000 vaccinees throughout 23 years, the incidence of acute encephalopathy caused by measles vaccine in this cohort can reasonably be described as very low.

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