Committee on Infectious Diseases

The Relationship Between Pertussis Vaccine and Brain Damage: Reassessment

Administration of pertussis vaccine has been associated temporally with local and systemic reactions, including febrile convulsions. Based on the National Childhood Encephalopathy Study (NCES), a large case-controlled, epidemiologic study in Great Britain, permanent neurological disability (brain damage) has not been considered a common sequela of rare, severe, adverse neurological events temporally related to pertussis immunization. Recently, however, reassessment of this conclusion has been prompted by the following events: a review of the NCES by a workshop convened to make recommendations for a possible future United States study of the association of pertussis vaccination and serious neurological illness, a legal decision in Great Britain questioning the findings of NCES; further investigations of the role of pertussis vaccine in causation of acute and chronic neurologic illness; and continuing reassessment of recommendations for pertussis vaccination by national committees in Canada, Great Britain, and the United States. Recent reviews and editorials also have addressed this and related questions concerning adverse events attributed to pertussis vaccine.

BACKGROUND

For several decades, most physicians believed that pertussis vaccine was a rare cause of serious neurological illness that could result in permanent sequelae or death. This belief was based on case reports and neurological manifestations in vaccine recipients, sequelae of pertussis disease, and adverse neurological events associated with smallpox and rabies vaccines. These observations, however, provide only circumstantial and, hence, potentially erroneous evidence about the association of pertussis vaccine and neurological sequelae. The following reasons illustrate why this association is difficult to establish.

First, the question of whether pertussis vaccine causes or is related only coincidentally to neurological illness in individual cases cannot be determined because (1) acute neurological illness can develop in children during the first year of life independent of immunization; (2) no specific clinical sign, pathological finding, or laboratory test exists that identifies an illness caused by diphtheria-tetanus toxoids-pertussis (DTP) vaccine; and (3) any assessment of whether vaccine recipients were impaired neurologically prior to immunization is complicated by the difficulty of determining whether infants younger than 6 months of age are neurologically normal.

Second, neuropathological changes in the brains of children who died of pertussis are most consistent with hypoxemia and vascular injury due to severe coughing paroxysms and are inconsistent with the concept that Bordetella pertussis is neurotoxic.

Third, the occurrence of neurological reactions after other vaccinations is not necessarily relevant because of differences in neuropathology, which can include perivascular demyelination associated with
a lymphocytic infiltrate. This finding indicates an immune complex-mediated process that differs from the nonspecific neuropathology in the brains of children whose fatal illnesses were related temporally to receipt of pertussis vaccine.\textsuperscript{10,16} The absence of distinguishing pathological findings is consistent with the lack of a unique or specific constellation of clinical findings defining a recognizable post-pertussis vaccine syndrome in children with alleged severe neurological reactions and subsequent manifestations of neurological injury.\textsuperscript{17}

In addition, the biological plausibility of a putative association between pertussis vaccine and neurological injury has not been demonstrated, and no acceptable animal model of biological mechanisms has been developed that demonstrates that pertussis vaccine causes neurological illness.

Thus, the major evidence incriminating pertussis vaccine as neurotoxic has been case reports in which differentiation between a coincidental and causative relationship is not possible. To determine the nature of this relationship, epidemiological studies are necessary. Because the risk of neurological events temporally related to DTP vaccination appears to be very low, if any, these studies must include a large number of children.

**THE NATIONAL CHILDHOOD ENCEPHALOPATHY STUDY**

The NCES was performed from 1976 to 1979 in Great Britain to address the issue of whether acute neurological illness associated with DTP immunization could result in permanent brain damage.\textsuperscript{13} This study used the case-control method to examine the causes and natural histories of serious acute neurological illness in a total of 1182 young children, aged 2 to 36 months, admitted to a hospital. Excluding children with infantile spasms, which were shown in separate analyses not to be attributable to DTP vaccine,\textsuperscript{18,19} 29 children (including 17 with prolonged convulsions and 10 with “encephalitis/encephalopathy”) had received DTP vaccine within 7 days of the reported onset of neurological illness. Analysis of the data from these cases and age-matched control children demonstrated a statistically significant association between the development of serious acute neurological illness and receipt of DTP vaccine within the preceding 7 days. The increased relative risk of acute neurological illness was 3.3 (95% confidence limits, 1.7 to 6.5).\textsuperscript{20} Follow-up 12 to 18 months later of previously healthy children immunized with DTP vaccine within 7 days before onset of the acute illness disclosed a small number with residual neurological abnormalities. Based on the population base of the NCES, the risks of acute neurological illness and resulting permanent brain damage in previously neurologically healthy children were estimated to be 1:140 000 and 1:330 000 immunizations, respectively, with wide confidence intervals.\textsuperscript{20}

Review of the NCES data, however, indicates that the study population used to estimate the risk of permanent brain damage was too small to draw valid conclusions. Only seven previously healthy children who appeared to develop neurological abnormalities following a DTP-related acute neurological illness were identified. Of these seven, six subsequently were found to have either alternative causes, such as Reye syndrome or viral infection, or were found not to be significantly neurologically impaired on follow-up.\textsuperscript{17} Furthermore, MacRae\textsuperscript{21} has noted that while the apparent relative risk of neurological sequelae for children with acute neurological illnesses in the first 7 days after DTP vaccination was increased, the relative risk was decreased in children whose DTP-related event occurred 7 to 28 days after immunization, and the relative risk of neurological sequelae for children suffering acute neurological illness more than 28 days after immunization was not increased. Most recently, a 10- to 12-year follow-up of the cases and controls in the NCES has been completed.\textsuperscript{22} The data are under review and complete analysis is not yet available.

In addition, in November 1989, after reviewing the NCES data to prepare recommendations for a possible similar study in the United States, a workshop at the Institute of Medicine sponsored by the Centers for Disease Control, concluded that because of the small number of cases on which the original conclusions were based and the study design limitations, the NCES could not provide valid information regarding whether DTP vaccine could cause permanent brain damage.\textsuperscript{1}

These findings, thus, indicate that pertussis vaccine has not been proven to be a cause of brain damage. Similar conclusions have been reached by the Canadian National Advisory Committee on Immunization\textsuperscript{7} and the British Pediatric Association.\textsuperscript{8} While the data accumulated to date may not prove that pertussis vaccine can never cause brain damage, they indicate that if it does so, such occurrences must be exceedingly rare. Furthermore, as previously noted, in individual cases the role of pertussis vaccine and acute neurological disease resulting in brain damage is impossible to determine on the basis of clinical or laboratory findings.
ADDITIONAL EPIDEMIOLOGICAL STUDIES

Other studies of the relationship between pertussis vaccine and neurological disorders have not provided evidence for a causal relationship between DTP vaccination and permanent neurological injuries. These studies include the following: (1) the North West Thames Study in England performed from 1975 to 1981, involving 134,700 children who each received three doses of DTP vaccine and 133,500 children who each received three doses of DT vaccine;23 (2) a case-control study in the Group Health Cooperative of Puget Sound of a cohort of approximately 36,000 children who received an estimated total of 106,000 doses of DTP vaccine from 1972 to 1983;5 and (3) a study of 38,171 Tennessee Medicaid children who received 107,154 doses of DTP vaccine from 1974 to 1984.6 Analysis of the results of a prospective 12-month, population-based, case-control study of acute neurological illness following an estimated 368,878 DTP immunizations during 1987 to 1988 in Washington and Oregon is currently in progress.24 Each of these studies individually is of insufficient size to provide definitive answers regarding rare events. While they indicate that pertussis vaccine can precipitate febrile seizures, the results of the three completed studies have not confirmed that pertussis vaccine is a cause of acute, serious neurologic illness and, therefore, it is unlikely to be a cause of chronic neurologic illness.

SEIZURES AND EPILEPSY

The estimated incidence of seizures occurring within 48 hours of administration of pertussis vaccine is 1:1,750, based on a study of 15,752 DTP immunizations given to children 0 to 6 years of age.26 Most postimmunization seizures are brief, self-limited, and generalized and occur in children who are febrile.23,25–27 These characteristics indicate that DTP-associated seizures are febrile convulsions, a relatively common disorder in early childhood that does not predispose children to epilepsy in most circumstances and has a generally benign outcome.28 Risk factors for seizures in DTP recipients include underlying convulsive disorders, personal history of a prior convulsion (unrelated to immunization), and a family history of convulsions.29,30

Examination of infants and children who previously experienced seizures following DTP immunization has not demonstrated an increased incidence of epilepsy or other neurological sequelae.4,23,26,27 In the studies of Tennessee Medicaid children and the Group Health Cooperative of Puget Sound, no evidence was found to suggest that DTP immunization predisposes a child to epilepsy.3,6 Another study in Denmark of approximately 150,000 children and 554 cases of epilepsy demonstrated no relationship between the age of onset of epilepsy and the scheduled age of pertussis immunization.5 This study and an earlier Danish report also confirm the findings of the NCES in demonstrating that pertussis vaccine is not a cause of infantile spasms.18,19 Thus, no evidence suggests that a seizure precipitated by DTP immunization increases the risk of epilepsy.

CONCLUSIONS

On the basis of these data, the American Academy of Pediatrics concludes that pertussis vaccine has not been proven to be a cause of brain damage. Similar conclusions have been reached by the Canadian National Advisory Committee on Immunization7 and the British Pediatric Association.8 These findings reaffirm the appropriateness of continued routine pertussis immunization of infants and children according to the recommendations of the American Academy of Pediatrics in the 1991 Report of the Committee on Infectious Diseases.31 The Committee will continue to review relevant data on this important topic, and revised recommendations will be issued as appropriate.
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REFERENCES

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