Neurologic complications in oral polio vaccine recipients

Between April 1982 and June 1983 four children 3 to 24 months of age were referred for evaluation of neurologic abnormalities found to be compatible with vaccine-related poliovirus infection, which had not been suspected by referring physicians. Patients were epidemiologically unrelated residents of Indiana, and none had prior symptoms suggestive of immunodeficiency. All had received poliovirus vaccine orally (first dose in three, fourth dose in one) and a diphtheria-tetanus-pertussis injection in the left anterior thigh within 30 days of symptoms. A vaccine-like strain of poliovirus was isolated from each patient, and each had symptoms (left leg paralysis in three; developmental regression, spasticity, and progressive fatal cerebral atrophy in one) persisting for at least 6 months. Immune function was normal in two with poliovirus type 3 infection, and abnormal (hypogammaglobulinemia, combined immunodeficiency) in two with type 1 and type 2 infection, respectively. The incidence of observed vaccine-related poliovirus infection in Indiana recipients of orally administered poliovirus vaccine was 0.058 per 100,000 per year, significantly greater (P <0.001) than predicted. (J PEDIATR 1986;108:878-881)

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Current knowledge of the risk of poliomyelitis and the rates of vaccine-associated complications is required to determine whether the live or the inactivated poliovirus vaccine is optimal for control of poliomyelitis.[1] In the United States, calculation of the risk of vaccine-associated complications has relied on practicing physicians recognizing and reporting cases to state and local health departments, and ultimately to the Centers for Disease Control. From 1969 to 1981, the "best available paralytic poliomyelitis case count" compiled by the CDC averaged four cases per year among recipients of orally administered poliovirus vaccine.[1] Although the risk to adult OPV recipients and adult contacts of vaccinees is recognized by most physicians, the risk to presumably healthy infant vaccine recipients is not generally appreciated. We have recently recognized four cases of vaccine-related neurologic complications in infant vaccine recipients. All four occurred between April 1982 and July 1983 in Indiana, a state with a population of 5.5 million. In each instance the referring physician failed to associate the neurologic abnormality

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BAPPCC	Best available paralytic polio case count
CT	Computed tomography
DTP	Diphtheria–tetanus toxoid–pertussis vaccine
IPV	Inactivated poliovirus vaccine
OPV	Orally administered poliovirus vaccine

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with administration of OPV; referring diagnoses included trauma in two, spinal cord tumor, and failure to thrive.

CASE REPORTS

Patient 1. In March 1983, this previously healthy 1-year-old boy had fever, irritability, and left leg weakness 22 days after the initial dose of DTP (left anterior thigh) and OPV. The onset of symptoms was associated with minor trauma. In the ensuing 4 days, fever resolved and he became unable to walk, crawl, or sit. On admission the only abnormality was flaccid left leg paralysis; sensation was normal. The cerebrospinal fluid contained 23 WBC/mm^3; glucose concentration was 54 mg/dl, and protein 131 mg/dl. Serum IgA was 69 mg/dl (normal 19 to 55 mg/dl), IgM 124 mg/dl (31 to 77 mg/dl), and IgG 796 mg/dl (442 to 880 mg/dl). Serum complement, T and B cell quantitation, T cell subsets, phytohemagglutinin lymphocyte stimulation, somatosensory evoked responses, and computed tomography of the head all yielded normal results. Poliovirus type 3 was isolated from stool and throat, and was characterized by the van Wezel and Hagendonk[2] method (performed at the CDC) as similar to Sabin strains. Serum obtained 3 to 10 weeks after paralysis had neutralizing activity of $\geq$1:40 against poliovirus type 3. A complement fixation antibody titer against *Mycoplasma pneumoniae* was 1:64, 1 week after admission, and had fallen to 1:8 within 21 days. Cold agglutinin titers were $\leq$1:4 in both serum specimens. Cultures for *M. pneumoniae* were not done. Two years later the leg flaccidity and muscle atrophy persisted; development and growth were otherwise normal. A complete series of IPV was given, after which neutralization titers to poliovirus types 1 and 3 were $\geq$1:40. Serum neutralizing antibody activity failed to develop during and after completion of the IPV series.

Patient 2. In April 1982, 2 weeks after receiving a fourth dose of DTP (left anterior thigh) and OPV, this 2-year-old boy had fever and left arm and leg weakness. Until this illness, the patient had been completely healthy and had never had any illness or infection suggestive of an immunodeficiency disorder. On admission 6 days later he had left hemiparesis, with greatest weakness in the leg. No other significant abnormalities were found on physical examination; normal lymphoid tissue was present. The cerebrospinal fluid contained 19 WBC/mm^3; protein concentration was 60 mg/dl, and glucose 71 mg/dl. CT of the head yielded normal findings. The ECG demonstrated a focus of slow activity in the right central and temporal regions. Poliovirus type 1 was isolated from the nasopharynx, and was characterized by the CDC as Sabin-like by the van Wezel technique. Sera obtained 1 and 2 weeks after the onset of paralysis had poliovirus type 1 neutralization titers of 1:10. Neutralization titers to types 2 and 3 were <1:10. Serum IgA was 2 mg/dl (normal 26 to 74 mg/dl), IgG 50 mg/dl (553 to 971 mg/dl), and IgM 12 mg/dl (27 to 73 mg/dl). Mumps and *Candida* skin tests produced reactions. Peripheral blood lymphocytes included 3% B cells; T cells, T cell subsets, and helper/suppressor ratio were normal. Two months later the left arm weakness had resolved and the ECG was normal. Flaccid paralysis and muscle atrophy of the left leg persisted. Intravenously administered gammaglobulin therapy was begun. The patient has remained in good health, with infrequent, mild respiratory tract infections, and the paralysis has persisted. He continues to require gammaglobulin supplements for humoral immunodeficiency.

Patient 3. This 9-month-old boy was referred for evaluation of failure to thrive and developmental regression in June 1982. At 6 months he sat alone, attempted to crawl, and babbled. He received doses of DTP and OPV at 4 months, and again at 6 months of age. At 7½ months he became listless, verbal activity decreased, and spontaneous use of the left arm and leg decreased slightly. Complete evaluation for failure to thrive and slow development at 8 months of age concluded with a diagnosis of cerebral palsy of undetermined origin. At admission he was alert, did not verbalize, and had spastic quadriparesis with decreased use of the left side. Cerebrospinal fluid, CT of the head, and nerve conduction velocities were all normal. An ECG showed mild generalized cerebral hemispheric dysfunction. Serum IgA concentration was <0.3 mg/dl (normal 19 to 55 mg/dl), IgG 7 mg/dl (442 to 880 mg/dl), and IgM 2.4 mg/dl (31 to 77 mg/dl). Blood lymphocytes were 16% T cells and 38% B cells; T cell subsets were 15% T4 and 28% T8. T cell response to phytohemagglutinin was markedly depressed. Poliovirus type 2, characterized by the CDC as Sabin-like, was recovered from stool and throat within 24 hours of tissue inoculation; high titers (10^8/ml) of poliovirus were recovered from both sites until death. Virus was not isolated from cerebrospinal fluid. The serum IgG was maintained at 400 to 600 mg/dl with intravenously administered gammaglobulin supplements. At 19 months, CT showed profound bilateral cerebral atrophy, most marked in the frontal and temporal regions. Neurologic and respiratory function progressively worsened, and the patient died at 21 months. Permission for postmortem examination was refused.

Patient 4. This previously healthy 3-month-old boy demonstrated left leg weakness in July 1983. He was referred to a community hospital for evaluation of a possible spinal cord tumor. Four weeks earlier he had received initial DTP (left anterior thigh) and OPV. The only abnormality at examination was flaccid left leg paralysis; sensation was intact. Lumbar puncture was not done. Poliovirus type 3 (CDC) was isolated from stool. Serum IgG concentration was 375 mg/dl (normal 311 to 549 mg/dl), IgA 49 mg/dl (8 to 34 mg/dl), and IgM 52 mg/dl (19 to 41 mg/dl). T cell numbers and function were normal. Neutralization titers against type 3 poliovirus were $\geq$1:32, 2 and 4 weeks after the onset of paralysis. Paralysis and left leg atrophy persisted at 18 months; growth and development have otherwise been normal.

DISCUSSION

The criteria used for including cases in the BAPPCC are illness clinically and epidemiologically compatible with poliomyelitis, paralysis, and persistent neurologic deficit after 60 days.[1] Patients 1, 2 and 4 fulfilled these criteria. Clinical and laboratory findings in our patients were comparable to those of the BAPPCC. The CDC reported a male/female ratio of 2.7:1 in vaccine recipients. Eleven of

the 37 vaccine recipients in the BAPPCC were immunodeficient, as were two (patients 2 and 3) of our four patients. Paralysis occurred in the leg in which the DTP was administered in our patients with paralysis; such localization of paralysis by wild polio infection after intramuscular injection has been reported.[3] No such data exist for vaccine strains. Paralysis was in a lower limb in 93% of the patients in the BAPPCC. Evidence for vaccine polio infection as the cause of illness in patient 3 is not definitive. This patient would not have fulfilled the criteria for inclusion in the BAPPCC. His findings were strikingly similar to those in a published report[4] of a child with combined immunodeficiency in whom progressive hypertonia and regression of social and motor development resulted from persistent poliovirus infection; poliovirus was isolated from throat and stool but not from CSF, which was normal. At autopsy, a strain of poliovirus type 2 with some disassociation of antigen and neurovirulence markers was recovered from brain tissue. Because permission for autopsy could not be obtained in our patient, and thus we were unable to examine or culture neural tissue, the diagnosis could not be firmly established.

The relative advantages and disadvantages of IPV and OPV have been extensively reviewed.[5] The major disadvantage of OPV is the potential risk of neurologic complications in vaccine recipients and susceptible contacts. The dramatic reduction of the number of cases of endemic and epidemic poliomyelitis in the United States has served to increase the proportion of cases that are vaccine associated. From 1971 to 1981, the BAPPCC included 153 cases of poliomyelitis.[1] Of these, 37 occurred in vaccine recipients, 56 in susceptible contacts of vaccine recipients, and 60 were either sporadic, imported, or epidemic cases that could not be associated with vaccine usage. The 37 neurologic complications among vaccine U.S. recipients yielded an annual incidence of 0.002 per 100,000 population. In Indiana, we observed an annual incidence of 0.058 per 100,000 ($P = 0.006$), remarkably higher than expected for the 15-month interval. The 1980 census estimated the Indiana birth rate to be 85,000 live births per year. A survey by the Indiana State Board of Health in 1980 reported that 88% of children younger than 2 years of age had received three or more doses of OPV. Based on a similar birth rate and immunization practices, the risk of neurologic complications among vaccine recipients younger than 2 years of age was approximately one in 37,500 for the interval during which our patients were observed. This differed with the estimate of two or three per million vaccinees reported by others.[6]

Physicians currently in practice in the United States may not recognize the symptoms of poliomyelitis or of vaccine-induced neurologic complications. The annual number of reported cases of poliomyelitis fell to fewer than 0.1 per 100,000 after 1965.[7] Inasmuch as more than 50% of physicians in practice in the United States completed training after 1965, many have not seen a patient with poliomyelitis.[8] If the diagnosis is considered, laboratory confirmation may be difficult for many practicing physicians. At the time of paralysis, antibody titers have often already peaked and a significant change in titer is no longer demonstrable. One or more strains of vaccine poliovirus may be excreted in the stool for several months after immunization. Because infection with other enteroviruses, and perhaps *M. pneumoniae*, may cause paralytic disease, culture and serologic tests for these pathogens should be performed to exclude these causes. Grist and Bell[9] reported that serologic confirmation of poliovirus infection in Scotland was most often requested by orthopedic surgeons or neurologists attending to late complications. Moreover, the facilities for viral cultures are not easily available to physicians in small community hospitals. Vaccine-related poliovirus infection may not have been considered in patient 3 if viral cultures had not been done. Although the association of complications with vaccine administration can usually be made with reasonable certainty by temporal association, physicians may be reluctant to do so without laboratory confirmation.

The current method of surveillance in the United States, that is, passive reporting of cases, may underestimate the frequency of vaccine-related complications. In other countries, active surveillance has been shown to discover cases more efficiently.[10] Finally, physicians may be hesitant to associate paralysis with the vaccine or to report vaccine-associated complications for fear of potential liability. Because major sequelae appear to affect the legs in most instances, surveillance directed at patients attending rehabilitation centers, brace shops, crippled children services, and specialists in neurology and orthopedic surgery might yield a higher incidence of vaccine-associated paralytic poliomyelitis. Perhaps the advisability of concomitant administration of DTP with OPV should be examined, or alternative vaccine regimens explored.

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