Minireview

Rotavirus Infection and Intussusception:
A View from Retrospect

Toyoko Nakagomi*

Department of Microbiology, Akita University School of Medicine, 1-1-1 Hondo, Akita, Akita 010-8543, Japan

Received May 10, 2000

Abstract: A live orally-administrable rhesus rotavirus (RRV) tetravalent (TV) vaccine, licensed in the U.S.A. and the European Union, was recalled from the market because it was suspected to increase the risk of intussusception during the week following immunization. In contrast, natural rotavirus infection is generally believed not to cause intussusception. Because my experience contributed to the first paper that linked intussusception with rotavirus infection, I have re-examined our own data published 22 years ago and other studies on this issue. I also made a case study of adenovirus and intussusception as a paradigm to establish an etiological association of viral infection and intussusception. My hypothesis postulated in this review is that natural infection of susceptible (or predisposed) infants with some rotavirus strains, probably serotype G3 rotaviruses, will result in an appreciable fraction of idiopathic intussusception. Thus, the number of rotavirus-induced intussusception cases may change reflecting the relative frequency of G3 strains, which I believe was much higher in the 70s than during the last two decades. The epidemiological data indicate that the RRV-TV vaccine triggers intussusception at a rate significantly higher than the background incidence rate following the week of vaccination, particularly after the first dose. In contrast, the data do not suggest that the cumulative incidence among the vaccine recipients increases accordingly, implicating that the risk of intussusception attributable to the RRV-TV vaccine may be minimal.

Key words: Rotavirus, Adenovirus, Intussusception, Live vaccines, Adverse reactions, Serotype, Attributable risk

Introduction

Rotavirus infections account for approximately 45% of severe diarrheal illness of infants and young children in both developed and developing countries (27). To put this into an actual number of cases per year in the United States, the culprit is estimated to cause 20–40 deaths, 55,000 hospitalizations and 500,000 physician visits, which costs in excess of one billion dollars (43, 44, 60). The outcome of infections is much more devastating in less developed regions of the world with estimated annual deaths totalling 600,000 (21).

A quarter of a century after the discovery of rotavirus as a human pathogen in 1973 (3), a live orally-administrable rhesus rotavirus (RRV) tetravalent (TV) vaccine (RotaShield®), developed by Wyeth Lederle Vaccines and Pediatrics, was licensed in 1998 by the U.S. Food and Drug Administration (FDA). The RRV-TV vaccine was then recommended by both the Advisory Committee for Immunization Practices (ACIP) and the American Academy of Pediatrics for universal immunization of U.S. children at 2, 4 and 6 months of age (8, 11). However, the ACIP declared a temporary halt of its use in July 1999 (7), followed by the withdrawal of recommendation in October 1999 (9). Although it is still licensed in the U.S.A. and the European Union, Wyeth Lederle withdrew RotaShield from the market and requested that all vaccine doses should be returned (63).

The issue of intussusception and rotavirus infection is something special to me because the patient I saw for the first time as a pediatric resident was a severe case of intussusception. A greater awareness of this disease made me feel that the cases of intussusception were

*Fax: 018-836-2607. E-mail: tnakagom@ipc.akita-u.ac.jp

Abbreviations: ACIP, Advisory Committee for Immunization Practices; CDC, Centers for Disease Control and Prevention; CI, confidence interval; FDA, Food and Drug Administration; NCKP, Northern California Kaiser Permanente; RRV, rhesus rotavirus; TV, tetravalent; VAERS, Vaccine Adverse Event Reporting System.
likely to cluster in the rotavirus season. It was 1974, the following year of Bishop et al's discovery of rotavirus. This experience was in the germ line of the publication of the first paper that positively linked intussusception with rotavirus infection (34). In this article, I will re-examine our own data and review the current consensus among specialists; i.e., (i) natural rotavirus infection does not cause intussusception, and (ii) the RRV-TV vaccine causes intussusception.

What Is Intussusception?

Pathologically, intussusception is defined as the invagination of one portion of the intestine into an adjacent segment of the intestine (intussuscipiens). The invaginated segment (intussusceptum) is drawn in half tone. One can get an idea of intussusception by mimicking the process with a disposable plastic umbrella sheath often found at the entrance of department stores, supermarkets or hospitals.

Clinically, intussusception is a pediatric emergency in infants of typically less than two years of age with its peak incidence at 3-9 months (12, 16, 17, 25), and characterized by intermittent colicky abdominal pain, vomiting, and the passage of stool mixed with blood and mucus (5). Abdominal mass is palpable in most cases. The diagnosis has been readily made by the "coil-spring" sign under barium roentgenography (Fig. 2), but ultrasonography has recently emerged as a sensitive and specific diagnostic tool for intussusception (15, 59, 62). Either barium enema or the pneumatic reduction technique is attempted as soon as the diagnosis is made in cases without complications. In cases in which non-invasive reduction techniques are unsuccessful, surgery is in order with or without resecting the affected segment of the intestine. Death may occur when there is delay in diagnosis or appropriate treatment, but mortality has declined to less than one percent in recent years (59).

Intussusception is a rather rare disease and its incidence varies depending on geographic location and study period (Table 1). A correct knowledge of the incidence of intussusception is important because it serves as an estimate for the background intussusception cases among those who received the RRV-TV vaccine. The most frequently cited figure in relation to the RRV-TV vaccine is from the rate of hospitalization for intussusception among infants aged less than 12 months during the period between 1991 and 1997 in New York, U.S.A., which is 51 per 100,000 infant-years (95% confidence interval [CI] = 48-54 per 100,000) (7, 50).
Rotavirus Infection and Intussusception: How the Story Begins

Following the first case of intussusception in October 1974, I had experienced an additional 33 cases of intussusception before the termination of my pediatric residency in Yamagata City Hospital (Saiseikan) in September 1976 (37) (Fig. 3). Barium enema, which was the routine procedure in those days, cured 8 of 10 patients and the remaining two patients underwent surgery including the first one. When I went over the literature, I felt that the pneumatic reduction technique was the one to try first. So, I tried this technique starting in January 1976. Unexpectedly, however, diarrhea followed in the first two cases after reducing the invaginated intestine with the pneumatic technique. Saiseikan Hospital served as the field for diarrheal stool specimens of Konno’s team, which had initiated a long-term survey of rotavirus diarrhea since December 1974 (31–33). Thus, there was a reason for me to suspect that the diarrhea in the intussusception cases (and intussusception itself) might be caused by rotavirus. Surprisingly, the stool specimens from the seven consecutive cases contained rotavirus particles when examined by electron microscopy (Fig. 3). This unexpected finding encouraged Konno’s team to continue the survey for the succeeding 15 months, and led to the observation that 11 (37%) of 30 cases with intussusception shed rotavirus in their stool while adenovirus was associated either serologically or by electron microscopy in 40% of the cases with intussusception. This observation was published by Konno, Suzuki, Kutsuzawa (my publication before 1982 was under the name of Kutsuzawa) et al in 1978 (34). However, two papers followed in 1982 reporting that only 8.3–9.3% of the cases with intussusception were associated with rotavirus infection (41, 42). Both papers therefore failed to confirm the association between rotavirus infection and intussusception that we had observed. More recently, Staatz et al (55) detected rotavirus in only 3 (3%) of 99 stool specimens from intussusception cases, and concluded that rotavirus does not play a causative role in intussusception. Furthermore, Rennels et al (50) reported the lack of an association between intussusception and rotavirus infection primarily because the winter-peak

Table 1. Incidence of intussusception

<table>
<thead>
<tr>
<th>Location</th>
<th>Study period</th>
<th>Incidence A</th>
<th>Incidence B</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newcastle, UK</td>
<td>1944–49</td>
<td>380</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>Birmingham, UK</td>
<td>1945–54</td>
<td>149</td>
<td>97</td>
<td>39</td>
</tr>
<tr>
<td>Newcastle, UK</td>
<td>1950–57</td>
<td>430</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Edinburgh, UK</td>
<td>1950–58</td>
<td>157</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>Aberdeen, UK</td>
<td>1950–59</td>
<td>219</td>
<td>116</td>
<td>57</td>
</tr>
<tr>
<td>Sheffield, UK</td>
<td>1950–59</td>
<td>227</td>
<td></td>
<td>51</td>
</tr>
<tr>
<td>Gothenburg, Sweden</td>
<td>1936–66</td>
<td>220</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Taipei, Taiwan</td>
<td>1955–64</td>
<td>77</td>
<td>57</td>
<td>10</td>
</tr>
<tr>
<td>Aberdeen, UK</td>
<td>1967–76</td>
<td>72</td>
<td></td>
<td>46</td>
</tr>
<tr>
<td>Auckland, NZ</td>
<td>1975–79</td>
<td>64</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Malmo, Sweden</td>
<td>12 years</td>
<td>250</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Buffalo, USA</td>
<td>1930–85</td>
<td>230</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>California, USA</td>
<td>1995–96</td>
<td>74</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>England, UK</td>
<td>1993–95</td>
<td>66</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>New York, USA</td>
<td>1991–97</td>
<td>51</td>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

a Incidence A: The number of cases per 100,000 live birth. Although the majority of cases occurred in children less than 1 year of age, this definition includes the intussusception cases that occurred in all age groups of children.

b Incidence B: The number of cases per 100,000 infants per year. According to this definition, only the number of cases in children less than 1 year of age is counted.

Fig. 3. Temporal distribution of the intussusception cases (34 cases including one recurrent case) that I experienced during my pediatric residency in Saiseikan Hospital, Yamagata, Japan. Electron microscopic examination of the stool specimens from patients with intussusception was initiated from the third case in January 1976, and continued through the following March. The barium enema technique was tried for the 10 cases encountered during the period between October 1974 and August 1975, whereas the pneumatic reduction technique was used starting in January 1976. After the introduction of the pneumatic reduction technique, the first two patients had diarrhea immediately following successful reduction. This experience triggered my suspicion that rotavirus causes intussusception, but the stool specimens from those patients were not tested for rotavirus. The shaded column represents the case in which rotavirus was found in the stool specimen, whereas the open column after January 1976 represents the case in which rotavirus was not found in the stool specimen.
pattern of the occurrence of rotavirus infection did not match the much evenly distributed occurrence of intussusception.

Konno et al’s study (34) contained two rotavirus seasons in its 15-month survey period. One may argue that this might have biased in favor of the increased incidence of rotavirus-associated intussusception cases. Such notion implies the possibility of nosocomial rotavirus infections. If so, could most of the cases be attributed to nosocomial infections of rotavirus? The clinical data I could find for the first four consecutive cases (the remainder was unavailable) indicate that diarrhea occurred on the day or the day following the onset of intussusception (i.e., on the day of admission). Serology showed a concurrent increase in rotavirus antibody titers for those who shed rotaviruses in their stool but not for those who shed adenoviruses. Thus, there is no indication to believe that nosocomial rotavirus infections were more likely to be the cause of diarrhea associated with intussusception than primary rotavirus infections.

Adenovirus: the Paradigm for Viral Infection and Intussusception

Since early on, it has been noticed that the single most common pathological finding of intussusception is lymphoid hyperplasia (45). Strang (58) first placed emphasis on the association of this pathological condition with newly identified adenovirus. When he reviewed 318 surgical cases of intussusception, Strang found mesenteric lymphadenitis in nearly half of the cases and speculated that the condition in the mesenteric lymph nodes reflected that of the lymphoid tissue in the wall of the intestine. Accordingly, he postulated a hypothesis that viral agents like adenovirus may cause intussusception when he noticed a paper (30) describing the isolation of adenovirus from patients with mesenteric lymphadenitis.

Once attention was directed to the association between intussusception and adenovirus, several studies followed where it was demonstrated that a significantly larger number of patients with intussusception (26.3–90.1%) shed adenovirus than patients with other diseases (2.6–6.2%) or healthy controls (0–8.0%) (1, 10, 18, 19, 48, 51, 52, 56). To take an example from Gardner et al’s study (19), the odds ratio for having intussusception in the adenovirus-positive group over the adenovirus-negative group is calculated to be 25.7 (95%CI=8.57–77.1), lending strong support for the role of adenovirus infection in the etiology of intussusception.

In addition, much direct evidence is available that indicates the presence of adenovirus in the lymphoid tissue of the diseased intestine. Yunis et al (64, 65) found adenovirus-like viral particles by electron microscopy and viral inclusion bodies by histology in a concurrent increase in rotavirus antibody in 12 of 15 cases of intussusception by *in situ* hybridization. As Bhikskul et al (2) reported, it is worthy of mention that the adenoviruses that are linked with intussusception are respiratory adenoviruses and not enteric adenoviruses (types 40 and 41). Anecdotal evidence is found in literature that severe adenovirus hepatitis followed after liver transplantation from a donor who had intussusception and had adenovirus in the appendix (61). Thus, studies carried out to date have established that approximately one-third of idiopathic intussusception cases are caused by adenovirus infection.

What Will Be Needed to Address the Question of Whether Intussusception Is Caused by Natural Rotavirus Infection?

The point that Konno et al (34) made is that concurrent rotavirus infections were documented in approximately one-third of the intussusception cases. This is a very high percentage comparable to that of adenovirus infections. This high percentage itself is suggestive of a strong association between rotavirus and intussusception. One often claimed drawback in our previous study is the lack of appropriate controls. So, I sought out data that could serve as a proxy (i.e., the number of rotavirus-positive patients hospitalized with diseases other than diarrhea during the one-year period between April 1978 and March 1979 in Saiseikan Hospital) (36). Of 441 control patients, only 10 shed rotaviruses in their stools. Thus, together with the data that 11 of 30 cases with intussusception shed rotavirus, one could calculate a “proxy” odds ratio, which is 25.0 (95%CI=9.40–66.5). This is as impressive a figure as that calculated for adenovirus in Gardner’s study (19) (see previous section).

In contrast to Konno et al (34), both Mulcahy et al (41) and Nicolas et al (42) found rotaviruses in only 8.3 and 9.3% of cases of intussusception, respectively. Staatz et al (55) found much less (3.0%). Could one conclude a negative association between rotavirus infection and intussusception from such low relative frequencies of rotavirus detection in intussusception cases? Let me take an example again from adenovirus to illustrate this point. One typical study shows that 3.1% of children
hospitalized with acute diarrhea shed adenovirus in their stool (23). However, such an observation denies in no way an etiological role of adenoviruses in childhood diarrhea. Furthermore, if one plots monthly numbers of adenovirus infections (all serotypes included) and compares this curve with the monthly occurrence of diarrhea cases, one will never find good correspondence. Would one ever conclude that adenoviruses are not associated with childhood diarrhea? Certainly not. Thus, if only a small percentage of idiopathic intussusception cases is attributable to rotavirus infections, the overall occurrence of intussusception cases will not fit the seasonal occurrence of rotavirus infection. The paradigm of adenovirus dictates that what is lacking in the rotavirus case is to detect rotavirus antigens or genome or both in the lymphoid tissue of the affected intestines from surgical cases. Unfortunately, such studies have never been performed to date.

Is only a small percentage of intussusception cases attributable to rotavirus infection? Curiously, in our previous study (34), the majority of rotavirus cases (7 out of 11) occurred in the first rotavirus season (corresponding to the second rotavirus season in Fig. 3), whereas only two rotavirus-associated cases were found in the second rotavirus season. The possibility of yearly variation in the number of rotavirus-associated intussusception cases is another point to consider. A 7-year study by Katsushima et al (29) performed in Saiseikan Hospital made this point: rotavirus-associated intussusception cases varied from 7.7 (1 case) to 40.9% (9 cases) where the number of all intussusception cases varied from 13 to 24. One explanation for this variation is that the pathogenic potential in inducing intussusception might be attributable to differences in circulating rotavirus strains. Different strains are known to circulate in different seasons (35). The serotypes of circulating strains may be one possible attribute that could explain the difference of the pathogenic potential of rotavirus strains. No serotyping methods were available, nor was isolation in cell cultures possible in those days. Unfortunately, no stool rotavirus specimens are available today. One final clue is to speculate serotypes from the RNA migration patterns (electropherotypes) of the rotavirus genomes on polyacrylamide gels. Electropherotyping of the rotavirus genome was a cutting-edge technology in the 70s (24), and fortunately I was involved in this type of work (38). Available pictures that contain electropherotypes of the rotavirus recovered from children with diarrhea in Saiseikan Hospital, Yamagata, in the 1974–1975 and 1975–1976 seasons. This is a composite figure, but, in each pair, two electropherotypes were originally from a picture on the same gel. Both electropherotypes, apparently identical, have a closely-migrating complex of gene segments 7, 8, and 9 (Fig. 4). Although the association of electropherotypes and serotypes is entirely observational, one can predict serotype G1 and G3 strains from their electropherotypes as described by Gouvea et al (22) (i.e., almost all G3 strains have closely-migrating segments 7, 8 and 9 on polyacrylamide gels) (26).

Assuming that serotype G3 rotaviruses are more likely to cause intussusception than other strains, a recognizable increase in the number of intussusception cases has to occur concurrently when serotype G3 rotaviruses become dominant. The last two decades have rarely seen the dominance of G3 rotaviruses in most studies performed in the world (35). Reviewing over 60 studies describing the distribution of G serotypes in the literature (35) revealed that serotype G3 strains were dominant in Texas, U.S.A., in the 1987–1988 epidemic season (22, 40). It would thus be interesting to examine whether the number of intussusception cases significantly increased in Texas during the rotavirus season in that year.

The RRV-TV Vaccine and Intussusception

The withdrawal and recall of RotaShield from the market by the manufacturer in consultation with the CDC and FDA has given the impression that the causal relationship between RotaShield and intussusception

![Fig. 4. Representative electropherotypes of human rotaviruses recovered from children with diarrhea in Saiseikan Hospital, Yamagata, in the 1974–1975 and 1975–1976 seasons. This is a composite figure, but, in each pair, two electropherotypes were originally from a picture on the same gel. Both electropherotypes, apparently identical, have a closely-migrating complex of gene segments 7, 8, and 9. Although purely observational, all G3 strains that I have encountered thus far have this pattern in common. Note that reference strain Wa has a faster moving gene segment, 9 (indicated with an arrow).](image-url)
was established with little ambiguity. However, the evidence from epidemiological studies available to me is arguable in one important aspect, if one would conclusively determine the role of the RRV-TV vaccine in the causation of intussusception and correctly evaluate the risk of intussusception attributable to the vaccine in the target population at large.

Before scrutinizing specific data, it is appropriate to summarize what made the regulatory authorities come to the decision to halt RRV-TV vaccination in the U.S.A. Available information has it that the temporal association between receipt of the RRV-TV vaccine and the occurrence of intussusception among the vaccinees is clear and statistically significant (i.e., the intussusception cases clustered during 3–7 days after receiving the first dose of the RRV-TV vaccine), and that the benefit from the vaccine does not outweigh the risk incurred by the vaccine when the burden of rotavirus disease in terms of the number of deaths is considered (i.e., the number of deaths in the U.S.A. attributable to rotavirus diarrhea is too small to justify the number of the intussusception cases caused by the RRV-TV vaccine). The former is the observation applicable universally, but the latter, the risk versus benefit ratio, depends on the settings in question. In this latter regard, the ACIP declared that its decision may not be applicable to other settings where the burden of disease is substantially higher and where the risks and benefits of rotavirus immunization could be different (9).

How Concerns about Intussusception Started

Concerns about intussusception as a potential adverse reaction go back to prelicensure field trials: 5 cases of intussusception occurred among 10,054 vaccine recipients and one among 4,633 placebo recipients, but the difference was not statistically significant (7). Three of the 5 cases among the vaccinees occurred within the week of receiving the RRV-TV vaccine (50). Accordingly, the ACIP recommended postlicensure surveillance for this adverse event following vaccination (7).

The Vaccine Adverse Event Reporting System (VAERS) Study

Approximately one million infants were vaccinated with the RRV-TV vaccine from September 1, 1998 through July 7, 1999. During this 10-month period, 15 cases of intussusception were reported to the Vaccine Adverse Event Reporting System (VAERS). Of these 15 cases of intussusception, 13 (87%) occurred after the first dose, and 12 (80%) developed symptoms within one week of receiving the RRV-TV vaccine (7) (Fig. 5). Given the background rate of intussusception among infants (less than 12 months) being 51 per 100,000 infant-years (i.e., 1.0 per 100,000 infant-weeks) (7, 50), it is estimated that the number of intussusception cases reported to VAERS fell within the range of what would be expected by chance alone during the week after receipt of the RRV-TV vaccine (7).

Since the publication of this early analysis of the

![Fig. 5. The number of confirmed intussusception cases among the recipients of the RRV-TV vaccine that were reported to the Vaccine Adverse Event Reporting System (VAERS) as well as from the Northern California Kaiser Permanente (NCKP) and Minnesota studies, according to the number of days from receipt of the vaccine to the onset of the disease. This chart is reconstructed from the data published in Ref. 7. While three cases scattered over the 2-month period in the NCKP study, 80% of the cases clustered during the first week of vaccination in the VAERS study. Clustering of the cases in the 3–7 day period was reproduced even after the cases reported to VAERS increased. In the Minnesota study, all cases occurred during the 2-week period after receipt of the vaccine.](image-url)
VAERS data in July 1999 (7), the number of intussusception cases reported to VAERS increased significantly, reaching 102 cases in October 1999 (13). At this point, the ACIP decided to recommend a halt of the RRV-TV vaccination to U.S. children (9), and the manufacturer, Wyeth Lederle Vaccines and Pediatrics, withdrew and recalled RotaShield from the market (63). The interim analysis of the intussusception cases reported to VAERS revealed that the cases clustered during the 3–7 day risk window period, particularly after receipt of the first dose of the RRV-TV vaccine, indicating a strong and significant relationship between the RRV-TV vaccination and intussusception (13).

Assuming that the figure from the New York study is applicable to calculate the background rate for intussusception among one million vaccinees, 10 infants would be expected to develop intussusception by chance within the week of receipt of the RRV-TV vaccine. Since approximately 60 cases were reported to have occurred within the week of vaccination, the attributable risk would be 50 (i.e., 60 – 10) per one million infants (or 5 per 100,000 infants) within the week of immunization. If this is the case, the next question is what the attributable risk of the vaccination would be over the entire observation period. Since VAERS is a passive surveillance system, there might be many unreported cases if intussusception occurred long after RRV-TV vaccination. Even if one assumes the actual number of the intussusception cases is twice as much as that reported to VAERS, the cumulative incidence of intussusception cases over the 10-month period among the RRV-TV recipients would not exceed the background incidence calculated from the New York study. Thus, the overall risk of intussusception attributable to the RRV-TV vaccine could be minimal.

**Managed Care and Other Cohort Surveys**

According to the postlicensure surveillance conducted at Northern California Kaiser Permanente (NCKP) over a 6-month period (December 1, 1998–June 10, 1999), 9 cases of intussusception were identified among infants aged 2–11 months: 3 were among 9,802 vaccinated children, whereas 6 were among never-vaccinated children (7) (Fig. 5). The rate of intussusception among children who had received the RRV-TV vaccine was 125 per 100,000 infant-years, and that among never-vaccinated children was 45 per 100,000 infant-years (7). The incidence in the never-vaccinated group was similar to that from the New York study (51 per 100,000 infant-years). Although both the age adjusted relative risk (reported as 1.9) and the vaccine-attributable risk (80 per 100,000 infant-years) suggest a strong association between the RRV-TV vaccination and the occurrence of intussusception, the number of cases among vaccinated children is too small to establish a statistically significant difference in the incidence of intussusception among vaccinated and unvaccinated children (7). The rate of intussusception within one week of receipt of the RRV-TV vaccine was calculated to be 314 per 100,000 infant-years or 6.0 per 100,000 infant-weeks, a figure very similar to that obtained by the VAERS study, but this is not statistically significant either (7).

In another study in Minnesota, over an 8-month period (November 1, 1998–June 30, 1999) 18 cases of intussusception were identified among infants aged 30 days–11 months, and 5 were among 54,478 RRV-TV recipients, whereas 13 were among unvaccinated children (7). As to the occurrence of intussusception cases during the risk window period, 3 infants developed intussusception during the week of vaccination and none after two weeks of receipt of the vaccine. Thus, the observed rate of intussusception within one week of receipt of the RRV-TV vaccine was 292 per 100,000 infant-years or 5.6 per 100,000 infant-weeks, again an apparently similar figure to that obtained by the NCKP study as well as that from the VAERS study.

The observation that the cases occurred within only 2 weeks of vaccination strongly suggests the causal relationship of the RRV-TV vaccine and intussusception. On the other hand, this survey also revealed that no intussusception cases occurred during the rest of the 8-month survey period, where 9 cases of intussusception would be expected if the rate of 51 per 100,000 infant-years (from the New York study) is applied to a cohort of the size of 36,318 infant-years. Since no information is available as to the size of unvaccinated cohort, it is impossible to calculate whether the cumulative incidence of intussusception among vaccinated children during the 8-month period exceeded that of unvaccinated children. Hence, it is also impossible to calculate the fraction of intussusception attributable to the RRV-TV vaccine.

**What Is the Risk of Intussusception Attributable to the RRV-TV Vaccine?**

To establish the overall risk of intussusception attributable to the RRV-TV vaccine is very important in illustrating what role the RRV-TV vaccine plays in the causation of intussusception and to make decisions in settings where the burden of rotavirus disease is high. The question is whether there would be any substantial increase in the incidence of intussusception after 1 year of follow-up if the RRV-TV vaccine were given to every infant in the birth cohort. The question can also be stat-
ed as whether the RRV-TV vaccine triggers intussusception soon after immunization only in those infants who are predisposed to develop the disease later in life irrespective of their receiving the RRV-TV vaccine. If this is the case (i.e., the fraction of intussusception cases in the target population attributable to the RRV-TV vaccine is minimal), would it be a correct decision that the RRV-TV vaccine should not be used even in countries where the burden of rotavirus is staggering?

Conclusion

While it is widely held that natural rotavirus infection does not cause intussusception and that the RRV-TV vaccine causes intussusception, it is too simplistic to believe so. My biased hypothesis is that natural infection of susceptible (or predisposed) infants with predominantly serotype G3 rotaviruses will result in some fraction of what is now known as idiopathic intussusception. The fraction of idiopathic intussusception cases attributable to rotavirus infection may change reflecting the relative frequency of G3 strains circulating among children, which I believe was much higher in the 70s than in the last two decades. As Kapikian used to put it, G3 was formerly the second most important human rotavirus serotype (28), but this has not been the case for the last two decades (35). Available epidemiological evidence strongly suggests that the RRV-TV vaccine triggers intussusception at a rate significantly higher than the background incidence rate following the week of vaccination, but does not appear to show that the cumulative incidence among the RRV-TV vaccine recipients increases accordingly. The RRV-TV vaccine may only bring the occurrence of intussusception a few months earlier, from the classical 3–7 months to 2–4 months of age without significantly changing the overall incidence of intussusception during the first year of life.

References

13) Cooper, M. (Reuters) Atlanta, Georgia, October 25, 1999. U.S. federal health panel withdrew its recommendation that infants be vaccinated against rotavirus.


