Absence of Exposure to Varicella Does Not Increase the Risk of Zoster

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(See the article by Gaillat et al, on pages 405–410.)

The remarkable new hypothesis put forth by R. Edgar Hope-Simpson, a general practitioner in Cirencester, England, in 1965 on the nature of herpes zoster was based on the observation of every case of herpes zoster by Hope-Simpson and his partner over 16 years in their practice of 3500 persons [1]. They recorded 192 cases of zoster during the 16-year period of 1947–1962, for an annual rate of 3.4 cases per 1000 persons. Because zoster presents such a dramatic and clean-cut clinical picture, he stated that they had no evidence for missing a single case. Hope-Simpson also pointed out the age-specific incidence of zoster, with the number of cases increasing after the age of 50 to 6.79 cases per 1000 population per year for the age group 60–69 years and to 10.10 cases per 1000 population per year for the age group 80–89 years. He also predicted that if a cohort of 1000 people lived to be 85 years old, 50% would have an attack of zoster and only 1 individual (1%) would have a second attack of zoster. The link between varicella virus and zoster was noticed in 1888 by von Bokay [2], and Hope-Simpson in 1954 found evidence by means of an epidemiologic approach in the Shetland Islands of Scotland that varicella and zoster had identity [3]. The ability of Weller and Stoddard in 1952 [4] to grow the varicella virus in tissue culture led to the proof in 1954 by Weller and Coons [5] that the virus from a patient with varicella and that obtained from a zoster patient were the identical varicella-zoster virus (VZV).

In his hypothesis of 1965, Hope-Simpson suggested that outbreaks of zoster were prevented by levels of neutralizing antibody to VZV and that 2 mechanisms stimulated antibody production and delayed outbreaks of zoster until after the age of 50: (1) subclinical reactivation of endogenous virus from the sensory ganglia and (2) exogenous exposure to the virus from a case of varicella or zoster provides a “boost” to the neutralizing antibody titer. This concept of exogenous boosting has been supported by results of 4 recent epidemiologic studies showing that repeated family and occupational exposure is associated with a reduced risk of zoster [6–9]. An unproven assumption of the exogenous boosting hypothesis that “repeated contact with varicella reduces the risk of zoster” is the converse idea that “the absence of contact with varicella causes an increased risk of zoster.”

To test this assumption, the team of investigators led by Gaillat et al [10] report in this issue of Clinical Infectious Diseases on an imaginative study designed to compare the frequency and age of onset of zoster in monks and nuns not exposed to children with those of the general population in France. The primary objective of the study was to compare the frequency of zoster in a population not exposed to children, such as members of contemplative monastic orders (CMOs) of the Roman Catholic Church, with that of the general population. Secondary objectives were to compare the reported age of onset of zoster in members of the CMO with that in the general population and to describe the frequency and age of onset of zoster in monks compared with nuns. A national, multicenter, observational comparative epidemiological study in an “exposed/nonexposed” design was conducted by using questionnaires. The authors applied rigorous standards to the questionnaires, and those who were members of monastic orders for <2 years or had zoster before entering the monastery were excluded. In France, varicella vaccine is not given to children, and by age 10 years, 90% of French children have acquired VZV antibodies by means of natural infection with VSV. To ensure that members of the CMO had not been exposed to VZV, all those who had regular contact with children aged <10 years were
excluded from the primary analysis population. A total of 1128 questionnaires were sent out to all monasteries.

The general population sample was constituted to be representative of the French population and to match the characteristics of the religious population. A predefined 3000 questionnaires were sent out to the general population. The questionnaire collected the following data: date of birth, sex, previous history of zoster, age or year of onset of zoster, confirmation of the diagnosis by a health care professional (physician), localization of the zoster, presence of other diseases at the same time as zoster, and pain following the disappearance of the zoster rash. Additional information collected from members of the CMOs included dates of entry to the monastery, activity, and history of regular contact with children aged <10 years.

No laboratory confirmation of zoster cases was carried out, and this might appear to be a weakness. All cases were confirmed by a physician. Hope-Simpson did point out, however, that the clinical picture of zoster is dramatic and classic, and a physician is unlikely to mistake the diagnosis [1]. No measures were taken to identify cases of a zosteriform eruption of herpes simplex virus.

The results of the study reported the frequency of zoster in the primary analysis population as 16.2% in the CMO members and 15.1% in the general population. The results focusing on the 10 years preceding the study showed a frequency of zoster of 6.4% among members of the CMO group, compared with 6.1% in the general population. The mean age of onset of zoster was 54.8 years in the CMO group and 48.6 years in the general population. None of these differences are statistically significant. The incidence of zoster was shown to increase with age in both groups and was greater in females than in males.

In summary, the study finds no association between the frequency and age of onset of zoster and a lack of exposure to varicella in a population of nuns and monks who had virtually no contact with children, compared with those in the general population. The authors rightly claim that this is the first study designed to evaluate an association between the increased risk of zoster in adults and the absence of contact with children with varicella. The results support the conclusion that this study with a long observation period showed no increase in the risk of zoster in adults not exposed to VZV.

The authors do state that the increasing risk of zoster with increasing age is mainly due to immunologic senescence with decreasing cell-mediated immunity to VZV in an aging population. A decline in VZV-specific cell-mediated immunity (CMI) with increasing age was first shown by Levin et al in 2003 [11]. They revealed by the use of an interferon-γ enzyme-linked immunosorbent spot-forming cell assay and a responder cell frequency assay that CMI declined with advancing age and could be boosted with a live attenuated high-dose VZV vaccine (OKA/Merck). When Hope-Simpson formulated his hypothesis, CMI and humoral immunity were not clearly differentiated. It is now clear that the immune component that is essential for protection against herpes zoster is VZV-CMI, and this declines progressively with increasing age [12]. When subclinical reactivation of endogenous VZV from the sensory ganglia occurs, the CMI of the aging immune system is not able to contain VZV replication and zoster occurs.

This study provides new evidence obtained by means of a creative and rigorous trial design to show that the absence of contact with varicella does not cause an increased risk of zoster. This could provide important information to support the argument that childhood vaccine programs against VZV will not lead to an increasing number of cases of zoster in young adults.

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References