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Polyomavirus SV40 infections in Kazakhstan

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Summary *Objectives*. To examine the prevalence of polyomavirus SV40 infections in Kazakhstan, a central Asian country known to have used potentially contaminated SV40 poliovaccines before 1962.

Methods. Cross-sectional study of 307 healthy volunteers from two ethnic groups (Kazakhs and Russians) in Almaty, Kazakhstan, from May through August 1999 using a specific SV40 plaque-reduction neutralization assay.

Results. Of the 307 volunteers enrolled in the study, 154 were Kazakhs and 153 were Russians. The overall prevalence of SV40 antibodies was 4.9%, and there was no significant difference between the ethnic groups ($p = 0.7$) or between males and females. The median SV40 neutralizing antibody titers in Kazakhs and Russians were 1:40 (range 1:10–1:500) and 1:20 (range 1:10–1:500), respectively. The median ages of SV40-infected Kazakhs and Russians were not different (42 vs. 24 years; $p = 0.1$), although there was a trend for increased seropositivity among older Kazakhs. There was no difference in SV40 positivity between those whose childhoods were spent in rural or in urban areas ($p = 0.4$). Importantly, 60% (9/15) of the subjects seropositive for SV40 were born from 1969 to 1980s, when poliovaccines were free from SV40.

Conclusions. This study showed evidence of polyomavirus SV40 infections in Kazakhstan, not only among individuals potentially exposed to contaminated poliovaccines, but in younger people not exposed to such vaccines. As increasing evidence indicates an association of SV40 with selected types of human malignancies, prospective studies are needed to examine the risk of SV40 infection with the development of neoplasias.

Introduction

Simian virus 40 (SV40) is a DNA tumour virus that is classified as a member of the *Polyomavirus* genus in the family Polyomaviridae.[1] The history of some SV40 infections in humans is linked to the

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development and distribution of early forms of the poliovaccine.[2–4] Both inactivated and live attenuated preparations of poliovaccine were made using primary rhesus monkey kidney cells, some of which were from animals naturally infected with SV40, a virus that was unknown at the time. Millions of people worldwide were inadvertently exposed to infectious SV40 from 1955 through early 1963 when administered SV40-contaminated vaccines;[4] these vaccines were used in several countries outside the United States, including the former Soviet Union and its republics, such as Kazakhstan.[4,5]

The neoplasias induced by polyomavirus SV40 in laboratory animals are predominantly brain cancers, mesothelioma, bone cancers, and lymphomas.[2,6,7] Evidence suggests that SV40 is an emerging human pathogen,[3,4] and a meta-analysis of published data involving 1793 cancer and 1649 control patients[8] indicated that there is a significant excess risk of SV40 associated with human primary brain cancers (odds ratio [OR] 3.8; 95% confidence interval [95% CI], 2.6–5.7), primary bone cancers (OR, 24.5; 95% CI, 6.8–87.9), malignant mesothelioma (OR, 15.1; 95% CI, 9.2–25.0), and non-Hodgkin's lymphoma (OR, 5.4; 95% CI, 3.1–9.3). Experimental data indicate that SV40 may be functionally important in the development of at least some of those human malignancies.[2–4,6–8] These data led the Institute of Medicine of the National Academies to conclude 'that the biological evidence is of moderate strength that SV40 exposure could lead to cancer in humans under natural conditions'.[3] Significantly, SV40 has been detected in cancers from children and young adult patients not exposed to contaminated poliovaccines.[2–4,8] Furthermore, the detection and recovery of infectious SV40 not only from tumours[9] but from non-neoplastic specimens[10–12] suggest that SV40 is causing infections in the human population today.

Kazakhstan is a large country in central Asia. Its population is known to have been exposed to potentially SV40-contaminated poliovaccines.[5,13] Kazakhstan has two major ethnic groups, one Asian in origin (Kazakhs) and the other Western (Russians). Each group constitutes approximately 40% of the country's population, and their socioeconomic conditions are similar. Albert Sabin provided original seed material of the three attenuated strains of poliovirus to the Institute of Poliomyelitis and Viral Encephalitis of the Academy of Medical Sciences of the USSR in Moscow in 1956 for the preparation of live, oral poliovaccines. Large preparations of vaccines were produced from the Sabin strains in rhesus monkey kidney cell cultures.[14] By December 1960, an estimated 77.5 million people throughout Russia and the USSR republics had been vaccinated, using over 263 million doses of monovalent or trivalent vaccines. This included 3.38 million recipients in Kazakhstan. Mainly children and young adults from the age of 2 months to 20 years were vaccinated, although in some regions older adults were immunized. In the Almaty region (Fig. 1), the former capital of Kazakhstan, then called Alma-Ata, vaccine was given to people up to 45 years of age. It is estimated that greater than 70% of all age groups from infants to 45 years in the Almaty region were immunized in 1959–1960. Children were vaccinated in Karaganda (Fig. 1), but there was only partial involvement of rural areas in Kazakhstan.[13,15] (These same vaccines were given also in 1959–1960 to over 10 million children under 15 years of age in Albania, Bulgaria, China, East Germany, Hungary, Korea, and Viet Nam.[13])

Inactivated poliovaccine was produced by the same Institute in Moscow using the Salk methodology and was used to vaccinate children in the USSR starting in 1957–1958. Many of these vaccines presumably were contaminated by SV40. Due to a large poliomyelitis outbreak in Almaty, Kazakhstan, persons there were vaccinated in 1958 with the killed vaccine.[15] SV40 was present in the Russian live poliovaccines. Viral tests carried out later suggested that the majority of the early vaccines were contaminated (estimated $>80\%$).[14] The SV40 titers detected in the poliovaccines ranged from about 10^3 to 10^4 infectious units/ml. After its discovery, SV40 was removed by plaque purification, followed by preparation of vaccines in kidney cells from *Cercopithecus aethiops* monkeys (not naturally infected with SV40) and heat treatment in the presence of $MgCl_2$.[14] Apparently, vaccines produced starting in 1962 were free from SV40 contamination. In this study, we examined the prevalence of SV40 infections in the two major ethnic populations (Kazakhs and Russians) in Kazakhstan to determine whether age, gender, or differences in childhood vicinity (urban or rural) affected the prevalence of SV40 viral infection.

Materials and methods

Study population

A cross-sectional study among unrelated healthy subjects was conducted in Almaty, Kazakhstan, from May through August 1999. Individuals between the ages of 11 and 69 years were enrolled after obtaining informed consent. Demographic information, household, environment, and socioeconomic