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Adverse Event Following Live Attenuated Chikungunya Vaccine in a Cynomolgus Macaque with Preexisting Chronic Hydrocephalus

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Introduction

Vaccination against chikungunya virus (CHIKV) is the primary means of preventing the emerging tropical vector-borne disease, with numerous groups currently working towards development and production of an immunogenic and protective vaccine for licensure (1). A notable recent effort utilizing an attenuated CHIKV with an engineered internal ribosome entry system (IRES) as a single administration (prime-only) vaccine has been shown to provide durable immunity and protective efficacy against infectious challenge in numerous animal studies (2–4). No significant adverse drug reactions (ADRs) have been reported in any of the animal vaccine trials using the IRES/CHIK attenuated viral vaccine to date. An animal with a preexisting, undiagnosed, subclinical but severe cerebral hydrocephalus was enrolled in a study of long-term immunogenicity of the IRES/CHIK vaccine. The cynomolgus macaque (*Macaca fascicularis*) began showing signs of neurological dysfunction 10 days post-vaccination, which progressed over the next several days, ultimately resulting in euthanasia. An underlying brain abnormality, chronic hydrocephalus, was revealed at necropsy and was subsequently investigated with gross and microscopic examination. This becomes the first reported case of an adverse event following administration of a live-attenuated CHIKV vaccine.

Case

The animal (8.2 y/o, 13.2 kg, male) was a purpose-bred cynomolgus macaque acquired from a commercial source and was screened for pre-existing antibodies to CHIKV and related alphaviruses prior to delivery. Upon receipt, the animal was thoroughly examined and screened for the presence of major viral and bacterial pathogens. Complete clinical diagnostics, including 12-analyte chemistries and CBC/differentials were performed; results were within normal limits. After enrollment in the study, the animal was intradermally administered the CHIK/IRES vaccine (1E+04 PFU in 0.5 ml saline) into the upper left deltoid. Approximately 10 days post-vaccination, the animal began showing clinical signs of

neurological dysfunction, including mild tremors and pronounced, unprovoked vocalization. Decreased appetite, facial pallor, and decreased activity ensued in subsequent days. Standard of veterinary care for nonhuman primates was initiated including supplemental nutrition and behavioral intervention. All diagnostic measures in clinical pathology outcome (e.g., CBC/differentials, clinical chemistries) showed no remarkable changes from prevaccination levels; however, weight loss after vaccination was apparent (–12% from prevaccination weight at euthanasia). Neurological signs progressed to include flaccid paralysis of the lower extremities, seizure, and behaviors consistent with distress; euthanasia was elected.

The animal received an immediate postmortem examination following euthanasia. Gross examination revealed severe, communicating hydrocephalus in the cerebral cortex located proximal to the left lateral ventricle duct (Figure 1A). The left occipital lobe meninges with a thin layer of attached parenchyma were adhered to a shallow depression in the overlying calvarium (Figure 1B). The corresponding left occipital lobe had only a thin layer of parenchyma remaining, which encompassed a large cavity filled with clear fluid with no apparent interruption of cerebrospinal fluid flow from the rest of the ventricular system. Microscopic evaluation of the lesion showed part of the cavity was lined by normal-appearing ependymal cells, suggesting that the fluid-filled space was produced by pressure from fluid originating within the ventricular system. In addition to normal appearing ependymal cells, a complete lack of inflammatory cells was noted within and surrounding the fluid-filled cavity suggesting that the defect and ensuing damage occurred several years prior, with a possible congenital etiology and/or trauma at or after birth. Subsequent immunofluorescent staining for toll-like receptor 2 (TLR-2) was performed to assess cellular activation. Immunofluorescent labeling of TLR-2 did not appear to be increased within the ependymal cells lining the fluid-filled cavity nor within the adjacent parenchyma (not shown). All other tissues examined, including vaccination site, were grossly normal apart from mild congestion in the right lung.

Discussion

To our knowledge, this is the first case describing unexpected, abnormal neurological clinical signs following administration of a live-attenuated vaccine in a susceptible nonhuman primate with a preexisting brain abnormality. Microscopically, the lack of inflammation and ependymal activation support the chronic nature of the lesion. This animal did not have detectable viremia post-vaccination; therefore, reversion of the vaccine is unlikely. An indirect effect of the vaccine cannot be ruled out, and raises the question whether pre-existing hydrocephalus increases risk of adverse vaccine events. If pre-existing hydrocephalus does increase risk, one question is whether increased risk is related to vaccine type (live-attenuated vs. inactivated) and/or virus type (neurotropic vs. non-neurotropic). CHIKV is not normally considered neurotropic although neurological disease is occasionally seen in perinatally-infected infants and the elderly. Other considerations include the effect of repeated anesthetic events in an animal with pre-existing hydrocephalus. Intracranial pressure slow waves, known as B waves, are reduced by 50% of wakefulness during general anesthesia and deep sedation (5). The reduction of the B waves has been shown to reduce intracranial compliance (5). Adverse events including neurologic signs have been reported post-anesthesia in humans with normal pressure hydrocephalus (6).

Hydrocephalus appears to be a rare event in nonhuman primates based on frequency noted at postmortem examination at the Tulane National Primate Research Center as well as reports published by other primate centers (7, 8). Reported causes of hydrocephalus in nonhuman primates include congenital and *in utero* trauma, drug exposure (e.g. triamcinolone acetonide), and viral exposure (e.g. Venezuelan equine encephalitis virus and Influenza virus) (7, 9–15). Frequencies of congenital abnormalities have been reported in nonhuman primates ranging from 0.3–1.65% with nervous and cardiovascular system being the most common (7). The onset and cause of hydrocephalus are unable to be determined in this case. Detection of hydrocephalus in humans is often aided by subtle to severe developmental delays as well as mentation deficits. Some of these subtle clinical signs may be more difficult to detect in nonhuman primates; therefore, other methods of antemortem detection may prove useful. Skull radiographs allow for antemortem detection of hydrocephalus; however, radiographs were not performed on this animal during experimental testing. In conclusion, the findings in this case report suggest the possibility of an increased susceptibility risk of unwanted adverse outcome associated with the use of live-attenuated CHIK viral vaccine in populations with preexisting conditions such as hydrocephalus.

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Figure 1.

(A) Brain; severe hydrocephalus in the occipital lobe of the cerebral cortex located proximal to the left lateral ventricle duct. (B) Calvarium; Meninges and a thin layer of occipital lobe parenchyma were adhered to the shallow depression within the calvarium corresponding to the fluid filled cavity within the left occipital lobe.