



Commentary to “A Case of Recombinant Coxsackievirus A2 Infection with Neurological Complications in Taiwan”

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Enteroviruses (EVs) are the predominant pathogens of most childhood illnesses. There are more than one hundred serotypes of EVs belonging to the genus *Enterovirus*, family *Picornaviridae*¹. These viruses were originally classified as polioviruses, coxsackievirus A (CV-As), coxsackievirus B, and echoviruses based on differences in cell tropism, infectivity, antigenicity, and pathogenicity². More recently, these viruses have been re-classified into four species (EV-A, EV-B, EV-C, and EV-D) based on their molecular and biological properties^{3,4}. The positive-stranded RNA genome of EVs has approximately 7,500 base pairs, and includes three genomic regions (P1, P2, and P3). The P1 region encodes four structural capsid proteins (VP1 to VP4), while the P2 and P3 regions encode seven nonstructural proteins (2A to 2C, and 3A to 3D). The VP1 capsid protein contains a number of neutralization antigenic sites which are used in virus serotyping⁵. Enterovirus EV-A71 has been reported to cause serious complications of the central nervous system, including encephalitis, meningitis, and poliomyelitis, and there have been several large outbreaks of EV-A71 worldwide in recent decades⁶⁻⁸. However, there are limited data on co-circulating non-EV-A71 EV-A strains, which are known to cause outbreaks^{9,10}.

Coxsackieviruses are subdivided into groups A and B on the basis of pathogenicity in suckling mice less than 48 hours old (group A caused flaccid paralysis and group B caused spastic paralysis)¹¹. Based on past experience, human infections with CV-As are generally mild with the exception of CV-A16. There are a few detailed reports describing the clinical features of coxsackievirus A2 (CV-A2). CV-A2 was previously thought to cause sporadic infections with benign clinical presentation, such as herpangina, and there have been reports of endemic episodes of CV-A2 in Taiwan between 2003 and 2005¹². A CV-A2 epidemic was reported to cause herpangina and hand, foot, and mouth disease (HFMD) among Taiwanese children in 2008¹³⁻¹⁴, including in two children who had complications of encephalitis and encephalomyelitis, and recovered without any sequelae¹³. Moreover, a natural recombinant CV-A2 was found in Hong Kong in four children with respiratory symptoms, two of whom died during the summer of 2012¹⁵. We previously reported a case of a 9-month-old girl with recombinant CV-A2 infection, who presented with herpangina with encephalomyelitis without long term sequelae¹⁶. This virus strain was thought to be closely related to the 2012 Hong Kong strain due to the high degree of genetic similarity shared between the two strains. To our knowledge, this was the first case which demonstrated that

the recombinant CV-A2 strain could present with central nervous system involvement.

It was previously reported that in the 2008 CV-A2 outbreak in Taiwan, most patients with CV-A2 infection presented with herpangina (84-94%) followed by HFMD, while younger patients mostly presented with respiratory symptoms^{13,14}. Febrile seizures were significantly more frequent in patients with CV-A2 infections (8.7%) compared to the general population¹⁴. Although uncommon, CV-A2 infection may be complicated with encephalitis and encephalomyelitis (1.1%) without long term sequelae¹³. Additionally, CV-A2 infection with transverse myelitis has been reported in Korea, 2014¹⁷, and in rare cases, patients presented with herpangina with encephalomyelitis. A previous study also reported an outbreak of acute intestinal infection caused by CV-A2, predominantly in Russia in 2010¹⁸. Based on these data, it is important to keep in mind that CV-A2 could be highly transmissible with a large variety of clinical presentations, such as herpangina, HFMD, respiratory or intestinal infections, and even neurological complications.

CV-A2 has been suggested to be the possible pathogen in some lethal cases, including a 15-year-old girl in Germany who had dual infection of CV-A2 and influenza virus B and died in 1969¹⁹. Reverse transcriptase-polymerase chain reaction (RT-PCR) and suckling mouse inoculation were used to detect an enterovirus sequence resembling CV-A2 in the stool and spleen of a 10-year-old girl who died suddenly with post-mortem findings of myocarditis²⁰. These findings suggested a causal link between CV-A2 and myocarditis. In 2012, Yip et al identified a recombinant CV-A2 in four young children with severe respiratory tract infection, two of whom died¹⁵. Although it could not be determined whether the virus was the cause of death, the data nevertheless suggested a strong pathogenic role for CV-A2.

Molecular epidemiology studies have demonstrated that circulation of different enteroviruses during outbreaks facilitates recombination of viruses^{21,22,23,24}, and this may play an important role in the evolution of enteroviruses. Recombination events have been described previously, especially in the non-capsid (P2 and P3) region of enteroviruses^{15,25,26}. In 2011, Hu et al reported that the CV-A2 (A2SD09) and CV-A4 (A4SZ09) strains had serotype-specific homology for the capsid proteins, but shared non-capsid sequences with each other, and the A2SD09 strain clustered with Mongolia strains isolated in 2003²⁵. Additionally, recombinant CV-A2 strains which caused death in a child in Hong Kong was shown to cluster with the EV-A71 sub-genotype B3 strain SAR/SHA66 in the P2 region, and with the CV-A4 strain SZ/CHN/09 in the P3 region, indicating possible recombination events in these regions. These studies indicated that genetic

recombination among CV-A2 strains may be a common evolutionary event. The limited number of complete modern EV-A genome sequences that are available, along with frequent viral recombination events makes it challenging to confirm the origin of these recombinant CV-A2 isolates. A comprehensive surveillance for enterovirus A strains, particularly CV-A strains, is needed to expand our understanding of the evolution of these co-circulating viruses.

In conclusion, the case that has been reported as due to CV-A2 infection (E2014041), possibly imported from Hong Kong, caused herpangina and neurological complications without sequelae in Taiwan in 2014¹⁶. This may be the first case which demonstrated that the recombinant CV-A2 strain could complicate with central nervous system disorders. Genetic findings suggested that this could be a particularly aggressive and neurotropic strain of CV-A2. CV-A2 is the predominant strain causing several endemic and epidemic outbreaks in Taiwan, and circulation of these viruses during outbreaks may facilitate viral recombination and the emergence of a virus causing a new disease manifestations. It is therefore important to institute a continued surveillance of CV-A2 circulation, based on modern genome sequencing, in order to monitor the molecular epidemiology of such outbreaks, and to track emerging recombination events.

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