

# Long Term Outcome and Cognitive Function After E71 CNS Infections

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The enterovirus 71 (EV71) outbreak in Taiwan in 1998 is very well-known to have caused a lot of HFMD, 405 severe and 78 fatal children cases. According to our previous clinical studies, symptomatic enterovirus 71 (EV71) infection can progress through four stages: HFMD/herpangina (Stage 1), CNS involvement (Stage 2), cardiopulmonary failure (Stage 3), and convalescence (Stage 4). Most EV71 cases in those studies stayed at stage 1, some progressed to Stage 2 and a few would advance to the most severe condition, Stage 3. We did autopsy for an EV71 fatal case. The brainstem pathology showed neuronophagia and immune-histochemical stain showed EV71 infected neurons, neuron loss. The most significantly risk factors associated with CNS involvement were fever $\geq$ 3 days and lethargy. Risk factors for pulmonary edema after CNS involvement are hyperglycemia, leukocytosis, and limb weakness. Hyperglycemia is the most significant prognostic factor for pulmonary edema.

In the follow-up study of severe EV71 cases, 18 (64%) of the 28 cases with cardiopulmonary failure after CNS involvement had limb weakness and atrophy, 17 (61%) required tube feeding, and 16 (57%) required ventilator support. Delayed neurodevelopment was found in only 1 (5%) case with severe EV71 CNS involvement and in 21 (75%) cases with cardiopulmonary failure ( $p<0.001$ ). Children with cardiopulmonary failure after CNS involvement scored lower on intelligence tests than children with CNS involvement alone ( $p=0.003$ ). Among patients with CNS involvement alone, children infected at ages younger than 2 had lower verbal comprehension than children infected at older ages ( $p=0.009$ ). EV71 CNS involvement with cardiopulmonary failure may be associated with neurological sequelae, delayed neurodevelopment and reduced cognitive functioning. Children with CNS involvement without cardiopulmonary failure did well in neurodevelopment. The rate of elevated attention-deficit/hyperactivity disorder-related symptoms among children with enterovirus 71 central nervous system infection was 20%, whereas that rate among matched control subjects was only 3%. They also had more internalizing problems. Enterovirus 71 central nervous system infection may affect long-term regulation of attention and emotion and cause hyperactivity-impulsivity in children.

In conclusion, most EV71 cases are HFMD and recovered. Some (possible 1%) progressed to Stage 2 encephalomyelitis, and 20-30% of cases with encephalomyelitis may progress to cardiopulmonary failure because of brainstem encephalitis and SIRS. Even under modern intensive care, 30% of them would die and many of the survivors would have neurological sequelae. After poliovirus was nearly eradicated by vaccination, EV71 is now considered one of the most important enteroviruses. Therefore, continuous surveillance of its occurrence, investigation of its virulence and its transmission are all warranted to improve the future control. Development of EV71 vaccine are ongoing and we hope for success in the near future.