

In Enterovirus 71 Encephalitis With Cardio-Respiratory Compromise, Elevated Interleukin 1 β , Interleukin 1 Receptor Antagonist, and Granulocyte Colony-Stimulating Factor Levels Are Markers of Poor Prognosis

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Background. Enterovirus 71 (EV71) causes large outbreaks of hand, foot, and mouth disease (HFMD), with severe neurological complications and cardio-respiratory compromise, but the pathogenesis is poorly understood.

Methods. We measured levels of 30 chemokines and cytokines in serum and cerebrospinal fluid (CSF) samples from Malaysian children hospitalized with EV71 infection ($n = 88$), comprising uncomplicated HFMD ($n = 47$), meningitis ($n = 8$), acute flaccid paralysis ($n = 1$), encephalitis ($n = 21$), and encephalitis with cardio-respiratory compromise ($n = 11$). Four of the latter patients died.

Results. Both pro-inflammatory and anti-inflammatory mediator levels were elevated, with different patterns of mediator abundance in the CSF and vascular compartments. Serum concentrations of interleukin 1 β (IL-1 β), interleukin 1 receptor antagonist (IL-1Ra), and granulocyte colony-stimulating factor (G-CSF) were raised significantly in patients who developed cardio-respiratory compromise ($P = .013$, $P = .004$, and $P < .001$, respectively). Serum IL-1Ra and G-CSF levels were also significantly elevated in patients who died, with a serum G-CSF to interleukin 5 ratio of >100 at admission being the most accurate prognostic marker for death ($P < .001$; accuracy, 85.5%; sensitivity, 100%; specificity, 84.7%).

Conclusions. Given that IL-1 β has a negative inotropic action on the heart, and that both its natural antagonist, IL-1Ra, and G-CSF are being assessed as treatments for acute cardiac impairment, the findings suggest we have identified functional markers of EV71-related cardiac dysfunction and potential treatment options.

Enterovirus 71 (EV71) is found globally, but since the mid-1990s, it has become a major public health

problem in the Asia-Pacific region, causing large outbreaks of hand, foot, and mouth disease (HFMD), which may be complicated by aseptic meningitis, encephalitis, fulminant cardio-respiratory failure, and sudden death [1]. Fatal cases are characterized by neurological involvement, with myoclonus, cerebrospinal fluid (CSF) pleocytosis, brainstem lesions on magnetic resonance imaging, and cardio-respiratory compromise; this manifests as poor peripheral perfusion, reduced cardiac contractility on echocardiography, and pulmonary congestion on chest x-ray radiograph [2].

The mechanisms underlying cardio-respiratory compromise in EV71 infection remain unclear. Because it is associated with brainstem encephalitis,

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