

## **REVIEW ARTICLE**

### **Enterovirus-associated neurological disease with special reference to enterovirus 71**

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#### *Abstract*

Enterovirus as a cause of neurological diseases is well known since the last century. Until recently, the poliovirus is regarded as the most important enteroviral cause of neurological disease in terms of its worldwide distribution, morbidity and mortality. With the anticipated eradication of poliovirus worldwide, its importance is gradually diminishing. The emergence of a non-polio enterovirus viz., enterovirus 71 to cause epidemic encephalitis in Eastern Europe in the 1970's drew attention to other members of the enterovirus group as causative agents of severe neurological disease. In the Asian Oceania region, in Malaysia, Taiwan, Japan, Australia and Singapore a recent reemergence of epidemic enterovirus 71 infection again focused attention on the enterovirus as an important cause of neurological disease especially in children. It serves as a timely reminder that the health threat from non-polio enteroviruses, which number more than 60 types, is considerable. Greater efforts must be made to counter this threat in the post-polio era, and to better understand the pathogenesis of neurological disease associated with non-polio enteroviruses.

*Keywords:* encephalitis, enterovirus 71

#### **INTRODUCTION**

Enteroviruses belong to the genus *Enterovirus* in the family **Picornaviridae**, so called because "picorna" is the shortened acronym for the original members of the group (poliovirus, coxsackie, orphan virus, rhinovirus), and the fact they are all **RNA** viruses.<sup>1</sup> At the same time "pico" used as a very small unit of measurement, fits in the nomenclature to designate very small RNA viruses, which typically describes members of the **Picornaviridae** family. Presently, the genus *Enterovirus* consists of more than 60 viruses that include poliovirus, coxsackie A and B, echovirus, enterovirus 70 and 71 (EV71)

The range of clinical syndromes associated with enteroviruses is legion and includes acute paralysis, aseptic meningitis, encephalitis, carditis, pleurodynia, conjunctivitis, hand foot and mouth disease and other enanthems<sup>1</sup>. While many of these diseases are relatively benign, others such as encephalitis and carditis may be fatal. A fascinating aspect of these clinical syndromes is that different enteroviruses may be associated with the same clinical syndrome. Conversely, the same enterovirus may cause different clinical syndromes. Moreover, these

associations are not always predictable: a given virus may behave differently, both clinically and epidemiologically, in different places at different times.

#### **ENTEROVIRUS 71 AND NEUROLOGICAL DISEASE**

Insofar as clinical syndromes involving the central nervous system (CNS) are concerned, those associated with poliovirus are perhaps the best characterised. CNS involvement may take the form of aseptic meningitis (non-paralytic poliomyelitis), paralytic poliomyelitis which may be spinal, bulbar or bulbospinal and finally polioencephalitis.<sup>1,2</sup>

Disease similar to paralytic poliomyelitis has been associated with many different non-polio enteroviruses mainly as sporadic cases.<sup>1</sup> However, epidemic poliovirus-type CNS involvement associated with EV71 is now well recognised since its first appearance in Bulgaria in 1975.<sup>3</sup> In the years that followed, outbreaks of EV71-associated CNS infections were regularly reported in Asia<sup>4</sup>, Europe<sup>5</sup> and Australia.<sup>6</sup> The most recent epidemics were in Asia occurring from 1997 to 2000, and involving

children in Malaysia<sup>7</sup>, Taiwan<sup>8</sup>, Japan<sup>9</sup>, Australia<sup>10</sup> and Singapore (personal communication: Dr WJ Shieh). In these countries, as elsewhere in the past, CNS involvement occurred in a background of EV71-associated hand, foot and mouth disease. Molecular analysis of viral genome in strains isolated in Malaysia, Japan, Taiwan did not appear to implicate a common source of infection.<sup>11</sup>

The pathological changes seen in the CNS of patients with fatal EV71 infection consisted of perivascular cuffing, parenchymal inflammation, microglial nodule and neuronophagia, features typically seen in most primary viral encephalitides.<sup>3,7,9</sup> Viral inclusion bodies were not detected however. Detailed neuropathological studies published in the recent literature showed that the distribution of inflammation appeared to be mainly confined to the spinal cord and brainstem, hence the term encephalomyelitis.<sup>12</sup> The inflammation was found to involve the entire spinal cord and medulla. In the pons, inflammation appeared to be limited to the tegmentum, sparing the base of the pons. In the midbrain inflammation extended throughout the parenchyma, sparing the cerebral peduncles. Milder inflammation was also seen in the hypothalamus, thalamus, cerebellar dentate nuclei and cerebral cortex. These findings are consistent with magnetic resonance imaging studies on many patients.<sup>9</sup>

The distribution of inflammation in EV71 encephalomyelitis has interesting similarities to bulbospinal involvement in paralytic poliomyelitis.<sup>13</sup> Unfortunately, it is not known if severe fatal encephalitis due to other non-polio enteroviruses takes the form of encephalomyelitis similar to EV71 since detailed neuropathological studies are hard to come by. This characteristic distribution of inflammation may suggest that virus enters the CNS via peripheral spinal and cranial nerves.<sup>14</sup> Other possibilities include neurotropism for specific groups of neurons in affected areas or infection via the autonomic system direct from the oral cavity and/or the gastrointestinal tract.

Immunohistochemical staining for EV71 was positive in peripheral processes and cytoplasm of morphologically normal and damaged neurons.<sup>15</sup> It was further observed that the distribution of positive neuronal staining was often less extensive than that of the inflammation suggesting that in addition to the direct viral cytolytic effect, other factors such as inflammatory mediators may contribute to tissue damage. Viruses such as adenovirus have been

suggested as possible cofactors in the pathogenesis of the disease<sup>16</sup>. Further work to determine the pathogenesis of CNS involvement and factors that determine enteroviral neurovirulence need to be done. This includes work with suitable animal models e.g. primates, and viral genome studies to determine sequences that may possibly contribute to neurovirulence.

The rapidity of death in some cases of EV71 infection was thought to be due to neurogenic pulmonary oedema secondary to destruction of the medullary centres that control cardiac and respiratory functions. The presence of pulmonary oedema, massive destruction of the medulla, and absence of myocarditis in these cases appear to support this hypothesis.<sup>7,9,17</sup> Other possible explanations include: a) the development of a capillary leak syndrome secondary to systemic viral sepsis, b) dengue shock syndrome-like illness which may have resulted when EV71 infection occurred in patients who had previously been infected by another enterovirus.<sup>18</sup>

## CONCLUSION

As we enter the new millennium, emerging and re-emerging epidemic viral encephalitides will continue to challenge clinicians and research scientists for years to come. Effective control measures and vaccination policies based on a sound understanding of disease pathogenesis have helped to control epidemic viral encephalitides such as those caused by poliovirus and Japanese encephalitis.<sup>19</sup> As the dangers of poliovirus infection subside and eradication becomes a reality, non-polio enteroviruses such as EV71 will continue to be important causes of neurological disease.<sup>20</sup> Indeed echovirus 7, not previously reported to be associated with epidemic encephalomyelitis, was discovered in some paediatric cases in Peninsular Malaysia recently (personal communication: Dr K B Chua). Neurologists, neuropathologists, virologists and neuroscientists must all work together to face the challenge of diagnosing viral encephalitis, identifying the infective agent involved and contributing more generally to a better understanding of the pathogenesis of this important group of disorders.

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