

**Review:**

## **The role of enterovirus in chronic fatigue syndrome**

**Journal:** *J of Clinical Pathology* 2005;58:1126-1132

**Author:** J K S Chia

**Correspondence to:**

Dr J K S Chia

CEI Research Center, 23560 Crenshaw Blvd 101, Torrance, CA 90505, USA;

E-Mail: [Chiasann-AT-pol.net](mailto:Chiasann-AT-pol.net)

**NLM Citation:** PMID: 16254097

**ABSTRACT**

Two and a half decades after coining of the term chronic fatigue syndrome (CFS), the diagnosis of this illness is still symptom based and the aetiology remains elusive. Enteroviruses are well known causes of acute respiratory and gastrointestinal infections, with tropism for the central nervous system, muscles, and heart. Initial reports of chronic enteroviral infections causing debilitating symptoms in patients with CFS were met with skepticism, and had been largely forgotten for the past decade. Observations from in vitro experiments and from animal models clearly established a state of chronic persistence through the formation of double stranded RNA, similar to findings reported in muscle biopsies of patients with CFS. Recent evidence not only confirmed the earlier studies, but also clarified the pathogenic role of viral RNA through antiviral treatment. This review summarises the available experimental and clinical evidence that supports the role of enterovirus in chronic fatigue syndrome.

**Abbreviations:** CFS, chronic fatigue syndrome; CVB, group B coxsackievirus; HHV-6, human herpesvirus 6; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; RT, reverse transcription

**Keywords:** enterovirus; chronic fatigue syndrome; double stranded RNA; viral persistence

[ ... ]

**DISCUSSION**

Taken together, these data suggest that enterovirus can initiate and perpetuate the immunological response often seen in patients with CFS. Smouldering viral infection of various cells of the body with continuous expression of double stranded RNA and viral antigens could result in a chronic inflammatory state in the local tissues and account for the diverse symptoms reported by these patients.

The mechanism of viral persistence reconciles the two seemingly opposing observations of the past two decades: absence of live virion in chronically infected patients and animals and the finding of enteroviral RNA in the blood or other tissues. The finding of double stranded RNA is consistent with the clinical symptoms of patients with CFS. Without forming double stranded RNA, our patients with HIV or

hepatitis B/C infections are usually not symptomatic, even though the measurable viraemia often exceeds 10<sup>4</sup>–10<sup>6</sup>/ml. In contrast, patients with CFS and the presence of viral RNA in peripheral blood leucocytes or in tissues, but without true viraemia, have debilitating symptoms; the severity of the symptoms correlated with the frequency of finding enteroviral RNA in the peripheral blood leucocytes (J Chia and A Chia. Detection of double-stranded RNA in the peripheral blood leukocytes of patients with the chronic fatigue syndrome. Abstract T-101. In: Program of the 104th General Meeting for the American Society of Microbiology. New Orleans: Louisiana, 2004). In most of the patients with CFS, the cyclic nature of low grade febrile illness and severe exacerbation after physical activity would be consistent with a cyclical pattern in the viral replicative activity.

It is probable that viral RNA found inside cells, in a stable double stranded form, can dissociate and replicate using viral RNA replicase; some of the positive strands, although restricted in replication,<sup>51</sup> are translated to viral proteins during active metabolic states (for instance, exercise), which subsequently perpetuates the immunological response, including but not limited to synthesis of specific neutralising antibody. Consistent with this hypothesis, a recent study on Sjögren's syndrome clearly detected enteroviral RNA and VP1 protein in minor salivary gland biopsies from these patients, but not in controls.<sup>52</sup> From the available data in the literature, however, it is not possible to exclude with complete certainty the possibility that a few virions are actually formed and sequestered in membrane vesicles within the infected human cells.

Among other immunostimulatory effects, double stranded RNA is a potent inducer of interferon synthesis, which activates intracellular RNase, with resultant degradation of excessive single stranded RNA. The finding of a higher level of RNase L activity in the mononuclear cells of patients with CFS is consistent with this paradigm.<sup>53,54</sup> However, enough positive and negative strands probably recombine to form stable double stranded RNAs, which are resistant to RNase L inactivation, and the life cycle will start again when the pressure of the immune response decreases. Ironically, the continuing inflammatory response towards persistently infected cells/tissues to halt viral infection may be partially responsible for the difficulty in finding viral genomes in these patients, and may also be responsible for the symptoms.

### **Take home messages**

- A severe flu-like illness occurs in most cases of chronic fatigue syndrome (CFS), suggesting that an infection triggers and possibly perpetuates this syndrome
- Common viral infections and unusual causes of CFS could be diagnosed based on the details of the initial flu-like illness, if present, epidemiological history, and early virological testing
- Different laboratories from Europe and recently from the USA have found enteroviral RNA in the tissues, including peripheral blood mononuclear cells and muscles, of patients with CFS
- Viral persistence through the formation of stable double stranded RNA reconciles the two opposing observations of the past two decades: (1) the absence of live virion in chronically infected patients and animals and (2) the presence of enteroviral RNA in the blood or other tissues

- Smouldering viral infection of various cells with continuous expression of double stranded RNA and viral antigens could result in a chronic inflammatory state in the local tissues, accounting for the diverse symptoms
- Interferon {alpha} and {gamma} act synergistically against enterovirus in vitro, and preliminary studies suggest that this combination may be an effective treatment for patients with chronic enteroviral infection

Self replicating double stranded RNA molecules (replicons) have been well studied and are currently used as vectors for DNA vaccines and drug susceptibility assays.<sup>55,56</sup> Double stranded RNAs can be extremely potent adjuvants for immune responses or, alternatively, these molecules with certain sequences may silence our genes by blocking our mRNA,<sup>57</sup> although the evidence for this last mechanism is not yet available for CFS.

**"Ironically, the continuing inflammatory response towards persistently infected cells/tissues to halt viral infection may be partially responsible for the difficulty in finding viral genomes in these patients, and may also be responsible for the symptoms"**

The paradox remains, however, that despite an ongoing immune response, these viral RNA infected cells are not eradicated. It is possible that viruses hide in long living, immunologically privileged cells, including but not limited to, macrophages, muscles, myocardial cells, and neurones,<sup>28–37</sup> although these cells are unable to produce much live viruses, perhaps, in part, because of the pressure from local interferon and high concentrations of neutralising antibody—a form of cryptic infection. Viral antigen has been identified in tissues by virus specific monoclonal antibodies but positive staining did not allow the differentiation between membrane bound viral proteins and sequestered virions.<sup>58,59</sup> Persistent infection of B cells and monocytes/macrophages, the cells initially responsible for the uptake/transport of virus, has been well described for other intracellular pathogens.<sup>60</sup> Recently, we have found enteroviral RNA in the bone marrow samples of two patients with CFS and cyclic neutropenia (JK Chia, unpublished observation, 2004), suggesting that stem cells in the bone marrow could be a source of ongoing viral infection, as reported in animal models of enteroviral infection.<sup>59</sup>

Thus, renewed interest is needed to study further the role of enterovirus as the causative agent of CFS. Many aspects of this research need to be addressed but there are three urgent priorities.

(1) To overcome the technical difficulties associated with the enteroviral RNA detection assay, because a reliable and reproducible measurement of cell associated viral RNA will provide a marker for antiviral treatment and provide conclusive evidence of chronic infection.

(2) To perform a proof of concept, randomised, double blinded, placebo controlled clinical trial investigating the efficacy of the combination of interferon {alpha} and {gamma}.

(3) To develop inhibitors for viral RNA replicase, the main mechanism for RNA replication, which allows the persistence of the viral genome in infected cells. In the future, a well designed, randomised, controlled trial of antiviral treatment will

ultimately provide crucial information on the pathogenic role of enterovirus in patients with CFS and other chronic diseases.

**ACKNOWLEDGEMENTS**

The laboratory work was supported by the Chu-Lee Tu memorial research fund.

© 2005 by BMJ Publishing Group Ltd & Association of Clinical Pathologists