

Letters

Enterovirus hypothesis for motor neurone disease

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EDITOR, — A longstanding hypothesis based on indirect and epidemiological evidence proposes that motor neurone disease is a late consequence of subclinical infection with poliovirus. C J Woodall and colleagues provide supportive evidence for this “enterovirus hypothesis,” reporting the finding of conserved enterovirus sequences in the spinal cords of nine of 13 patients with motor neurone disease when they used conventional polymerase chain reaction and hybridisation; they conclude that these sequences were related to Coxsackie B virus rather than poliovirus.¹ The enterovirus hypothesis has also been proposed for idiopathic inflammatory myopathy, and Behan and Behan, from the same group as Woodall and colleagues, have reported finding enterovirus in 56% of cases of idiopathic inflammatory myopathy (27/48).²

In conjunction with our study of the prevalence of enteroviruses in idiopathic inflammatory myopathy³ we investigated 28 patients with sporadic motor neurone disease and seven matched controls, using quality RNA extracted from either frozen or paraffin sections from the spinal cord, brain stem, and motor cortex. In contrast to the results of Woodall and colleagues, we found that none of the patients or the controls were positive for enterovirus sequences in a sensitive, nested polymerase chain reaction assay.³ The duration of disease, degree of autolysis of tissue, and time for which the tissue had been stored in paraffin were all excluded as factors that may predispose to negative results.

We have previously discussed³ the difference and consequences of the locations of primers between our enterovirus assay³ and that established by Gow et al⁴ and now applied to motor neurone disease.¹ In brief, both assays use primers that recognise sequences of the conserved 5' untranslated region of the enterovirus genome and, indeed, show a marginal overlap of 61 bases. Although a deletion downstream of our primer EV2³ could conceivably explain the anomaly between the results of these two studies, the consequence of such a deletion or specific mutation would most probably be to inhibit viral growth and perhaps attenuate neurovirulence as has been described for mutations and deletions in the 5' untranslated region of the poliovirus genome (for example, Sabin strains). Nevertheless, Woodall and colleagues could easily confirm such an alteration in the 5' untranslated region of the enterovirus genome in their patients positive for enterovirus by using anchor polymerase chain reaction.

With regard to persistent enteroviral infections and idiopathic inflammatory myopathy, three recent studies⁵ in addition to our own³ have found no evidence of enterovirus RNA in muscle tissue despite each assay differing in its polymerase chain reaction format or primer combinations within the 5' untranslated region of the enterovirus genome; having verified broad specificity for enteroviruses including Coxsackie B viruses; and

showing adequate sensitivity, which in our assay was 40-400 copies (12.5-125 ag) of synthetic Coxsackie B virus RNA transcripts in 1 µg of cellular RNA. Moreover, in one of these studies an unspecified number of patients with motor neurone disease were included in the control group of 16 subjects and no enterovirus infection was detected by polymerase chain reaction.⁵

The enterovirus hypothesis for the pathogenesis of both motor neurone disease and idiopathic inflammatory myopathy seems unlikely, given that most polymerase chain reaction results are negative, unless there has been appreciable alteration of the 5' untranslated region of the enterovirus genome.

References

- 1.Woodall CJ, Riding MH, Graham DI, Clements GB. Sequences specific for enterovirus detected in spinal cord from patients with motor neurone disease *BMJ* 1994;**308**:1541-3. (11 June.)
- 2.Behan WMH, Behan PO. The role of viral infection in polymyositis, dermatomyositis and chronic fatigue syndrome. In: Mastaglia FL, ed. Inflammatory myopathies. London: Bailliere Tindall, 1993:637-57.
- 3.Fox SA, Finklestone E, Robbins PD, Mastaglia FL, Swanson NR. Search for persistent enterovirus infection of muscle in inflammatory myopathies *J Neurol Sci* 1994;**125**:70-6.
- 4.Gow JM, Behan WMH, Clements GB, Woodall C, Riding M, Behan PO. Enteroviral RNA sequences detected by polymerase chain reaction in muscle of patients with postviral fatigue syndrome. *BMJ* 1991;**302**:692-6.
- 5.Leon-Monzon M, Dalakas MC. Absence of persistent infection with enteroviruses in muscles of patients with inflammatory myopathies. *Ann Neurol* 1992;**32**:219-22.