the absence of RCTs, a case-control study design may help to approximate the issue.

In summary, because most of the healthcare insurance money is spent during the last weeks of a patient's life, prognostic data as provided by Nieuwkamp *et al*¹ are critical. On the basis of their results, investigators can only be inspired to set up an RCT or a case-control trial to further clarify this important question.

J Neurol Neurosurg Psychiatry 2006;**77**:900–901.
doi: 10.1136/jnnp.2006.095182

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Received 3 May 2006

Revised version received 3 May 2006

Accepted 6 May 2006

Published Online First 17 May 2006

Competing interests: None declared.

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Hidden encephalitis

Lock and key approach to “hidden” encephalitis

E J Thompson

Further keys to unlock diagnosis and treatment to “hidden” encephalitis can be obtained by access to PCR and IgG immunoblotting

Although varicella zoster virus is notorious for masquerading in various clinical presentations (eg, Guillain-Barré syndrome, Bell's palsy or even without the shingles rash), it nevertheless remains a completely curable disease, provided the suspicion of the neurologist is raised.¹ To clinch the diagnosis requires access to possibly two laboratories, thereby adopting a dual approach to both antibody and antigen (lock and key)—namely, viral immunoglobulin G (IgG) and polymerase chain reaction (PCR). The recent report by Sindic *et al*² (see p 938) admirably shows such an approach. They have confirmed the principle that early in the disease (first week) the virus predominates, but then antibody synthesis begins. Thus, the PCR test for antigen is positive in 62% (8/13) of cases during the first 7 days, but the viral-specific IgG thereafter becomes 83% (10/12) positive.

Continuing research into the technology of PCR has yielded further improvements, and in parallel there have also been important steps forward

in defining the specificity of the IgG response to viral and other infections. By using more refined examination of the qualitative immune response—for example, oligoclonal bands—it has also been possible to greatly improve the sensitivity of IgG assays and also the signal-to-noise ratio using better isoelectric focusing technology. This has allowed us to extend our examination of the total IgG population and then to just focus specifically on individual viral or other antigens and their corresponding patterns in the parallel cerebrospinal fluid and serum samples. This side-by-side comparison has been the bedrock to define local synthesis of IgG in the central nervous system, and thus it has also been a major step beyond the simple quantitative determination of IgG levels in cerebrospinal fluid and serum, as these do not distinguish any important clonal characteristics of the antibodies.

The same general notion of comparing PCR and IgG has also been found for other viruses, as shown in a large

national study of encephalitis in Finland.³ The authors showed 5.1% (133/2590) positive cases using PCR; however, using IgG assaying 7.7% (245–3173) positive cases were identified. A more recent case review of a much smaller number of patients with herpes simplex virus encephalitis emphasised the importance of viral IgG (4/4 positive) assaying to complement PCR (5/6 positive).⁴

For best practice, it is hoped that adequate paraclinical support will be available to neurologists, which gives them access to the laboratories (for both PCR and viral IgG immunoblotting), thus producing further keys to unlock considerably more diagnosis and treatment of “hidden” encephalitis.

J Neurol Neurosurg Psychiatry 2006;**77**:901.
doi: 10.1136/jnnp.2005.095547

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Published Online First 5 June 2006

Competing interests: None declared.

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