SHORT REPORT

No clinical evidence of hidden vCJD in UK children

C M Verity, A M Winstone, L Stelitano, A Nicoll, R G Will

Arch Dis Child 2006;**91**:608–609. doi: 10.1136/adc.2004.071266

Between May 1997 and November 2004 this national prospective surveillance study identified 1007 children with “progressive intellectual and neurological deterioration” (PIND). In most cases specific diagnoses were made, but of 92 undiagnosed children with PIND 46 had died and only four underwent full necropsy. There was no clinical evidence of variant Creutzfeldt-Jakob disease (vCJD) in these undiagnosed cases, but without necropsy it is not possible to exclude vCJD completely.

Recently it was reported that preclinical variant Creutzfeldt-Jakob disease (vCJD) had been detected in a patient who was heterozygous (methionine/valine) at codon 129 of the prion protein gene (PRNP).¹ All previously identified cases of vCJD had been methionine homozygous at codon 129 of PRNP. The case highlighted the need for continuing national surveillance for vCJD.

The first cases of vCJD were identified in young adults,² raising the possibility that children might develop the disease. In May 1997 we began active national surveillance for vCJD in children less than 16 years old through a monthly surveillance card that is sent to all consultant paediatricians in the United Kingdom by the British Paediatric Surveillance Unit (BPSU). Paediatricians are asked to report patients with “progressive intellectual and neurological deterioration” (PIND) because this group of children is likely to include any cases of vCJD. The surveillance team gathers clinical information about PIND cases from local clinicians—there is no contact with the families. An expert group of paediatric neurologists independently reviews the anonymised case histories and classifies the PIND cases by diagnosis when possible. If vCJD is suspected on the basis of the PIND surveillance, it is suggested that the local paediatrician obtains consent to refer the case to the National CJD Surveillance Unit (NCJDSU) in Edinburgh for full investigation. Full details about our study including the PIND case definition and the criteria for confirming vCJD are given in a previous publication.³

Ethical consent for the PIND study was obtained from the Cambridge local research ethics committee and from the Public Health Laboratory Service (now Health Protection Agency) ethics committee.

Between May 1997 and November 2004, clinical information was available for 1007 children who met the criteria for PIND (fig 1). There were six children with vCJD, who were notified to the PIND study between 1998 and 2001. They were also referred to the NCJDSU and diagnosed as probable or definite vCJD. Their clinical presentation was similar to that described in older patients with vCJD and all have died. The youngest was a girl who developed symptoms at 12 years of age.

There were 758 PIND children with a confirmed diagnosis other than vCJD. In these children there were 114 known neurodegenerative conditions, which illustrates the

complexity of classifying children with PIND; 151 children were still under investigation.

The investigations in the 92 undiagnosed cases cannot all be listed here, but to give an example, 77 of them had magnetic resonance imaging (MRI) of the brain (table 1); none was reported to show the “pulvinar sign” that is characteristic of vCJD,⁴ and many showed abnormalities not described in vCJD. In the case of one Asian child the MRI report was unavailable as the family had moved. Fifteen of the undiagnosed children did not have MRI, but 11 of these had brain computed tomography (CT), with eight showing abnormalities (such as cerebral or cerebellar atrophy) that are not typical of vCJD. Four cases had neither CT nor MRI but in all of these the siblings had been investigated without a diagnosis.

Our study emphasises that an obstacle to the detection of vCJD in children is the small number of necropsies that are done, even in those who tragically die of progressive neurodegenerative disease of the 92 undiagnosed PIND cases, 46 had died and only four underwent full necropsy. This is a dramatic example of a problem that is reported in other branches of paediatrics.⁵

The only way to diagnose vCJD with certainty is by neuropathological study. It is therefore not possible to exclude vCJD completely in the undiagnosed PIND children who died without a full necropsy. On the other hand these children had been carefully investigated by their paediatricians and they did not have the reported features of vCJD. The undiagnosed PIND cases are a heterogeneous group and we could find no sign of a previously unrecognised syndrome emerging among them. Our surveillance shows that the majority of PIND cases are diagnosed during life without the need for a necropsy or neuropathological study. We are therefore fairly confident that vCJD has not been missed in PIND children reported to us.

Seven years is a relatively short time in which to study the epidemiology of a new disease with an unknown incubation period. The recent discovery of preclinical vCJD in a PRNP heterozygous patient raises the possibility that other heterozygous patients may develop vCJD, possibly with a new phenotype.

There is still no screening test for vCJD, and the PIND study provides the only means of actively seeking cases of vCJD among the many rare causes of progressive neurological deterioration in children. Despite the limitations that are inherent in this type of surveillance,³ the study continues to provide unique epidemiological data.

ACKNOWLEDGEMENTS

The PIND study is funded by the Department of Health. Many thanks to all the paediatricians who have reported cases, to Mr Richard Lynn, the Scientific Coordinator of the British Paediatric Surveillance Unit of the Royal College of Paediatrics and Child Health, and to members of the Expert Group: Professor Jean Aicardi, Dr Peter Baxter, Dr Stuart Green, Dr Michael Pike, Professor Richard Robinson, Professor Robert Surtees, and Dr John Wilson.

Abbreviations: PIND, progressive intellectual and neurological deterioration; vCJD, variant Creutzfeldt-Jakob disease

Figure 1 Children notified between May 1997 and November 2004 who met the study criteria for progressive intellectual and neurological deterioration (PIND) (n = 1007).

Authors' affiliations

C M Verity, A M Winstone, L Stelitano, Addenbrooke's Hospital, Cambridge, UK

A Nicoll, Communicable Disease Surveillance Centre, London, UK

R G Will, National Creutzfeldt-Jakob Surveillance Unit, Western General Hospital, Edinburgh, UK

Correspondence to: Dr Christopher M Verity, Child Development Centre, Box 107, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK; christopher.verity@addenbrookes.nhs.uk

Accepted 17 May 2005

Published Online First 31 October 2005

Table 1 Ninety two cases of progressive intellectual and neurological deterioration (PIND) with no diagnosis

MRI done (n = 77)

MRI result unavailable: 1

MRI normal: 22

MRI abnormal: 54

atrophy cerebral hemispheres: 16

atrophy cerebral hemispheres plus other abnormalities: 12

white matter abnormal: 12

white matter abnormal plus cerebral atrophy: 6

white matter abnormal plus other abnormalities: 1

cerebellar atrophy or hypoplasia: 6

focal abnormality in basal ganglia: 1

MRI not done (n = 15)

CT done in 11

CT normal: 3

CT abnormal: 8

cerebral atrophy: 5

cerebral and cerebellar atrophy: 1

basal ganglia calcification: 1

thalamic calcification plus cerebral infarction: 1

CT not done in 4 (see text)

CT, computed tomography; MRI, magnetic resonance imaging.

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