Variant Creutzfeldt-Jakob disease

Citation for published version:

Digital Object Identifier (DOI):
10.1136/bmj.38804.511644.55

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
BMJ

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.
WHAT IS ALREADY KNOWN ON THIS TOPIC

The evidence base for prescribing drugs to children lacks sufficient Pharmacokinetic and pharmacodynamic data.

Adult doses are often extrapolated to children without taking account of potential differences in drug handling with age or dose requirements for effectiveness.

Licensing data for paediatric dosing are often sparse, and subsequent studies may result in important changes to recommended doses.

WHAT THIS STUDY ADDS

HIV infected UK and Irish children have been underdosed with antiretrovirals in the past nine years.

Poor pharmacokinetic data at licensing results in incorrect drug dosing until important pharmacokinetic results emerge after licensing and inform revision of dosage recommendations.

Guidelines stating alternative dosage strategies (by weight or surface area) for the same drug lead to different and inconsistent doses.

Inadequate dosing also arises through failure to adjust for ongoing growth.

The United States have recently committed to promoting research specific to children’s medicines while protecting children as participants in clinical trials. The UK Department of Health has launched the Medicines for Children Research Network (http://www.mrc.ac.uk/mcrn), which aims to develop closer links between the drugs industry, regulators, families, and paediatricians, links that will be needed to meet the challenges of developing and manufacturing appropriate paediatric drugs (http://www.hivforum.org).

The Collaborative HIV Paediatric Study (CHIPS) is a collaboration between the Medical Research Council Clinical Trials Unit, UK, and the National Study of HIV in Pregnancy and Childhood (NSHPC) at the Institute of Child Health, London. Committees and participants are on bmj.com.

Contributors: See bmj.com.

Funding: CHIPS is funded by the London HIV Consortium and in the past has received additional support from Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Roche, Abbott, and Gilead.

Competing interests: None declared.

Ethical approval: UK multicentre research ethics committee and relevant local research ethic committees.


Variant Creutzfeldt-Jakob disease: prion protein genotype analysis of positive appendix tissue samples from a retrospective prevalence study

James W Ironside, Matthew T Bishop, Kelly Connolly, Doha Hegazy, Suzanne Lowrie, Margaret Le Grice, Diane L Ritchie, Linda M McDardle, David A Hilton

Abstract

Objective To perform prion protein gene (PRNP) codon 129 analysis in DNA extracted from appendix tissue samples that had tested positive for disease associated prion protein.

Design Reanalysis of positive cases identified in a retrospective anonymised unlinked prevalence study of variant Creutzfeldt-Jakob disease (vCJD) in the United Kingdom.

Study samples Three positive appendix tissue samples out of 12 674 samples of appendix and tonsil tested for disease associated prion protein. The patients from whom these samples were obtained were aged 20-29 years at the time of surgery, which took place in 1996-9.

Setting Pathology departments in two tertiary centres in England and Scotland.

Results Adequate DNA was available for analysis in two of the three specimens, both of which were homozygous for valine at codon 129 in the PRNP.

Conclusions This is the first indication that the valine homozygous subgroup at codon 129 in the PRNP is susceptible to vCJD infection. All tested clinical cases of vCJD have so far occurred in the methionine homozygous subgroup, and a single case of probable iatrogenic vCJD infection has been identified in one patient who was a methionine/valine heterozygote at the valine codon 129.

This article was posted on bmj.com on 10 April 2006: http://bmj.com/cgi/doi/10.1136/bmj.38804.511644.55
this genetic locus. People infected with vCJD with a valine homozygous codon 129 PRNP genotype may have a prolonged incubation period, during which horizontal spread of the infection could occur either from blood donations or from contaminated surgical instruments used on these individuals during the asymptomatic phase of the illness.

Introduction

In a prevalence study for variant Creutzfeldt-Jakob disease (vCJD), we identified three appendices that stained positively for disease associated prion protein (PrP). We looked at 12 674 specimens (11 109 appendices, 1565 tonsils) removed from 1995-2000. Most of the patients (83%) were aged 10-30 years at the time of operation. This number of positive results is greater than would be predicted from the numbers of patients diagnosed with vCJD in the United Kingdom (161 to date). Furthermore, the annual incidence of new cases of vCJD has declined from a peak in 1999. As all patients with vCJD belong to the methionine homozygous subgroup, determined by the codon 129 polymorphism in the prion protein gene (PRNP), one possible explanation for this apparent discrepancy could be a different PRNP genotype in the three positive cases (the prevalences of PRNP codon 129 genotypes in the general UK population are about 40% methionine homozygous, 10% valine homozygous, and 50% heterozygous). This possibility was supported by a slightly different pattern of immunoreactivity in the second and third positive appendix cases in comparison with clinical cases of vCJD. We recently identified a case of asymptomatic vCJD infection that seemed to have been transmitted by red cell transfusion in a PRNP codon 129 heterozygote, demonstrating that the methionine homozygous genotype is not uniquely susceptible to vCJD infection.

Results

For both cases the genotype was confirmed as homozygous for the valine allele (VV) (figure). This method has been previously validated and was controlled in our laboratory by studying the PRNP codon 129 polymorphism in both paraffin embedded sections and frozen tissues from 25 other cases.

Discussion

These results give the first indication that PRNP codon 129 valine homozygotes may be susceptible to vCJD infection. Though the immunohistochemical technique used in our earlier study seems to be specific for disease associated prion protein, it is unlikely to be 100% sensitive, suggesting that the true prevalence of vCJD infection in the UK population may be even higher than earlier estimated. Genetic studies of kuru, another orally transmitted human prion disease, found that PRNP codon 129 MV and VV genotypes were associated with longer incubation periods than the MM genotype. As the ethical approval for our study placed restraints on the identification of individual cases, we are not able to state with certainty the age of the patients in the positive cases at the time of surgery. We can, however, state that they were aged 20-29 years at the time of surgery, which took place in 1996-9. No clinical cases of vCJD at any age have yet been identified in PRNP codon 129 valine homozygotes, indicating the need for continued surveillance of all cases of vCJD in the UK.
What is already known on this topic

A recent prevalence study of accumulation of prion protein (as a marker for vCJD infection) in appendix and tonsil specimens in the UK found 3/12 674 positive cases, which is more than expected from the current number of clinical cases of vCJD.

What this study adds

Analysis of DNA from two of the three positive samples found them to be valine homozygotes at codon 129 in the prion protein gene, indicating that this genetic subgroup (which is a different subgroup from that in which all cases of vCJD have so far occurred) is susceptible to vCJD infection.

Individuals with this genotype may have a prolonged incubation period with subclinical infection and could secondary spread of vCJD by blood transfusion or surgery.

Though it is inadvisable to overinterpret the data from only three positive cases in this study, it is perhaps surprising (given the relative prevalences of PRNP codon 129 genotypes in the general population) that both the positive cases analysed here were valine homozygotes. Though this may represent a chance finding, we should consider the possibility of differences in the peripheral pathogenesis of vCJD that depend on the PRNP codon 129 genotype. The patient who developed asymptomatic vCJD infection after red blood cell transfusion was a codon 129 heterozygote in whom both tonsil and appendix tissues were negative for staining for disease associated prion protein with identical methods as used in this study, though the spleen and lymph nodes gave positive results. PRNP polymorphisms in sheep infected with scrapie also have a major influence on the incubation period and timing and distribution of disease associated prion protein in lymphoid tissues during the incubation period.

A prolonged incubation period after infection with vCJD is likely to result in an asymptomatic carrier state (which cannot yet be identified), which represents a potential risk for horizontal transmission of vCJD infection by blood transfusion, blood products, or contaminated surgical instruments. These uncertainties further underline the need for continued surveillance of vCJD in the UK (including surveillance for subclinical or asymptomatic infection), a requirement to continue to reduce the possibility of secondary iatrogenic transmission, and the inclusion of carrier states and susceptibility to vCJD infection in all PRNP codon 129 genotypes in future disease modelling.

Contributors: JWI (guarantor) and DAI were responsible for the prevalence study and the analysis of the results, including the selection of the cases for analysis, and drafted and modified the manuscript. MTB established the methods for DNA extraction and analysis, designed and executed the validation study, and drafted and modified the manuscript. KC and DH performed the DNA extraction on the test materials and in the validation study and modified the manuscript. MLE, SL, DLR, and LM-C identified cases for the validation study and prepared the paraffin sections for DNA analysis and modified the manuscript.

Funding: The prevalence study was funded by the Department of Health (1216963 DAH; 1216982 JWI). Competing interest: None declared.

Ethical approval: The prevalence study received approval from the South and West multi-centre research ethics committee (MREC reference 99/6/32) and for each of the centres included, appropriate local research ethics committee approval.

10 doi 10.1136/bmj.38804.511644.55