

# New-variant Creutzfeldt–Jakob disease

CREUTZFELDT–JAKOB disease (CJD) is a rare neurological disorder with associated dementia, which was first described in the early 1920s and has now been found worldwide with similar incidence rates to the United Kingdom (UK). It occurs more frequently in late middle-age (mean age at death = 63 years)<sup>1,2</sup> and has varying incubation periods, thought to be between five to 15 years. The symptoms are progressive dementia and it is usually fatal within six months.

New-variant CJD (nvCJD) was first discovered in March 1996 by the CJD Surveillance Unit.<sup>3</sup> By November 1999, 47 cases of nvCJD had been identified in the UK and one case in France.<sup>2</sup> The current incidence of nvCJD is less than 5% of the total number of CJD cases.<sup>1</sup>

This previously unrecognised variant of CJD appears to present in a much younger population (mean age at death = 29 years).<sup>1,2</sup> A factor that led to its recognition was its prolonged duration, with sufferers surviving up to 23 months after its onset.<sup>1</sup> The median delay between the onset and confirmation of the diagnosis is 15 months.<sup>4</sup> There appears to be no obvious relation to occupation and there has been no increase in the rate of occurrence of cases.<sup>4</sup> Two cases have had a definite history of blood transfusion and previous surgical operations have been postulated as a possible aetiological factor.<sup>4</sup>

The early symptoms of nvCJD vary from other forms of CJD, in that there are non-specific symptoms of unexplained illness,<sup>5</sup> such as anorexia,<sup>6</sup> mild insomnia,<sup>5</sup> apathy,<sup>5</sup> mood swings, and possible personality changes,<sup>6</sup> but a lack of prominent neurological signs.<sup>4</sup> In nvCJD a striking psychiatric symptom reported in 12 cases was unsustained delusions.<sup>6</sup> Early neurological symptoms can include: paraesthesiae in lower limbs and face, lack of co-ordination, difficulty in walking, unusual aches and pains in hands, feet, face, and lumbar region, and a strange taste in the mouth.<sup>1,5-8</sup>

The later stages of nvCJD are more akin to those of the terminal stages of other forms of CJD.<sup>5</sup> The symptoms often include: uncontrollable jerky movements, limb stiffness, incontinence, dysphagia, loss of awareness of surroundings, agitation, a permanent frightened look in the eyes, possible hallucinations and delusions, and, eventually, dementia (which will ultimately overshadow other psychiatric symptoms), akinetic mutism, and, in some cases, cortical blindness.<sup>5-8</sup>

Difficulties occur in diagnosis, as the early symptoms of nvCJD are often non-specific. These symptoms may last up to several months in a patient who, even after this period of time, will not have been labelled as having nvCJD<sup>9</sup> because of similarity with other neurological and psychiatric diseases. Families may suffer a great deal of distress through the progression of the disease owing to the current inability to provide a definitive diagnosis. Families observe the slow decline in the patient's mental state, knowing that the only treatment for nvCJD is palliative as there is no known cure.<sup>1</sup> One relative of a nvCJD sufferer described her family's feelings: "we're being destroyed by a man-made disease".<sup>10</sup>

The causative agent of this disease is thought to be abnormal prion proteins (PrPs). PrPs are normal constituents of mammalian cells, although their specific function is unknown, but the introduction of abnormal protease-resistant PrPs is thought to bring about a conformational change in the normal form.<sup>11-13</sup> This produces large numbers of abnormal PrPs that accumulate in lymphoreticular tissue before invading neural cells, disrupting

normal cell function, and eventually leading to cell death.<sup>11,13,14</sup> PrPs are proteins that are resistant to accepted sterilisation procedures<sup>11-13</sup> and are also thought to be responsible for related transmissible spongiform encephalopathy (TSE) diseases in animals, including bovine spongiform encephalopathy (BSE) and scrapie.<sup>1</sup>

New-variant CJD can only be definitively diagnosed at post-mortem and is characterised by spongiform changes in the brain. Studies initiated by the UK Department of Health (DoH) of the use of ante-mortem diagnostic tools have proved initially successful. The first study suggests the analysis of tonsil and appendix tissue for the accumulation of abnormal prions,<sup>14</sup> while a second is investigating the use of magnetic resonance imaging to highlight thalamic changes in the brain caused by nvCJD.<sup>15</sup>

The cause of nvCJD is almost certainly due to exposure of the population to BSE-infected beef products that first occurred in the 1980s. This hypothesis is strongly supported by transmission studies on mice, which have confirmed that BSE and nvCJD are both caused by the same strain of PrP.

The latest report of a case in a 24-year-old mother has raised the possibility that transfer from mother to baby may be possible. Recent findings by the DoH showed that, from an investigation of 3000 samples of tonsil and appendix tissue, all samples were free from abnormal prions.<sup>16</sup> However, the risk of an epidemic cannot be dismissed. It may be many years before an accurate assessment of risk can be made because of what appears to be a prolonged incubation period in comparison with other forms of CJD.<sup>17</sup>

As with many rare diseases, the problem of diagnosing a case such as this is that it is usually considered an area for the hospital specialist. Instead, in the event of an established case the primary health care team can lend considerable support to the patient and their carers. This can be in the form of providing access to honest and appropriate information on treatment and prognosis or in the provision of long-term palliative care.

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## UTI antimicrobial resistance: tricky decisions ahead?

THERE are major and justified concerns about the overuse of antibiotics.<sup>1,2</sup> General practitioners (GPs) prescribe 80% of antibiotics, hence control of antibiotic resistance depends greatly on rational prescribing behaviour by these doctors.<sup>3</sup> In a recent study, overall antibiotic prescribing rates in practices correlated with antibiotic resistance rates in urine samples from those practices,<sup>4</sup> suggesting a direct link between antibiotic prescribing in general practice and antibiotic resistance. There is also concern that antibiotic prescribing may increase demand in the health service by encouraging reattendance.<sup>5</sup> It is important to understand why GPs prescribe antibiotics; after all, they have extensive experience of making such decisions and it would be surprising if they did not reflect on outcomes.

In this month's *Journal*, Fenwick *et al*<sup>6</sup> employ a decision analysis model to assess different strategies used by GPs in managing women suspected of having uncomplicated urinary tract infection (UTI). Empiric prescribing of antibiotics at initial contact was the most cost-effective strategy, confirming the findings of Barry *et al*<sup>7</sup> in the United States. This is chiefly because, on balance, women recovered more quickly if given an antibiotic, and near-patient tests (NPTs), such as nitrite and leucocyte esterase strips, are imperfect.<sup>8</sup> A 'wait and see' approach denies early treatment to the 50% of patients whose infections will not resolve spontaneously within three days. Cranberry juice has been advocated as an alternative,<sup>9</sup> but is of unproven benefit.<sup>10</sup> The authors address the issue of antibiotic resistance recommending urine dipstick testing prior to treatment as a strategy which, although sub-optimal in health economic terms, considerably reduces antibiotic prescribing. Kolmos<sup>3</sup> advocated urine microscopy performed by GPs in their surgeries, a test commonly employed in Denmark; however, there are training and resource issues that make this impractical in the United Kingdom.

The decision analysis model used for the current study considered financial costs, but decisions in medicine may be made at other levels. There are deontological considerations of a doctor's duty to do what is best for an individual, utilitarian issues as to what is best for society, and there are even decisions made at the level of what is best for the doctor. These different levels of decision-making help explain disagreement about which strategy is optimal. In addition, decisions in medicine are often complex and it may be difficult to apply evidence from clinical trials to the circumstances of an individual patient.<sup>11</sup>

In managing uncomplicated UTI in women, cost minimisers will choose empiric prescribing of antibiotics.<sup>6</sup> If one emphasises

the doctor's duty to do what is best for an individual, you might empower the patient to decide whether or not issues surrounding antibiotic resistance should influence the prescribing decision but point out the likelihood of a speedier recovery with antibiotics. In the current climate, to do the greatest good for the greatest number the emphasis might be on providing both cost-effective health care and reduced antibiotic prescribing. Indeed, Coast<sup>12</sup> considered including antibiotic resistance as a cost in economic evaluation. If doctor factors are important you might minimise the number of consultations and adopt strategies to reduce risk of litigation.

In a qualitative study of GPs' views about antibiotic prescribing, doctors prioritised their duty to an individual patient. 'Most felt that the evidence from clinical trials was not watertight and that antibiotics may help some patients. Although a minority mentioned bacterial resistance as a potential problem this was seen as a community issue, whereas the GPs' priority was the well being of the individual patient.'<sup>13</sup> Also, parents may feel validated by a prescription of an antibiotic to their child — a powerful influence.<sup>14</sup>

Just as fashions in ethics change, it is important to be clear about the decision analysis framework used to make a case. For example, in a randomised double-blind trial Dagnelie *et al* found a one- to two-day benefit of treatment with penicillin V in patients clinically suspected of having group A  $\beta$ -haemolytic streptococci acute sore throat.<sup>15</sup> The authors wrote: 'Treatment may be beneficial with regard to the clinical course but is not necessary'. In a recent study, Zwart *et al*<sup>16</sup> found a benefit of 2.5 days with one week's course of penicillin V if patients had group A  $\beta$ -haemolytic streptococcal infection (half of the cases recruited in their series). In an editorial following Zwart *et al*'s paper, Del Mar<sup>17</sup> states 'this benefit is so modest that one could dispute its clinical importance'. Many sufferers might disagree.

The editor of the *BMJ* wrote on the subject of antimicrobial resistance: 'We may have to give up our antibiotics for minor infections just as we may have to give up our cars for unimportant car journeys'.<sup>18</sup> There is little evidence of people changing the way they use their cars because of utilitarian considerations. Also, it is difficult to define what constitutes a minor infection; tonsillitis can cause fever, toxicity, and difficulty maintaining adequate fluid intake. Complication rates are low, but sore throats are very common.<sup>19</sup> A Medical Research Council Bulletin,<sup>20</sup> prepared prior to Zwart *et al*'s paper,<sup>16</sup> indicated that there was little evidence for the use of antibiotics, yet still suggested using them in patients who were very ill. As with minor

infection, there was no definition of what constitutes 'very ill'.

There should be unbiased debate about antibiotic use. Doctors are likely to consider their duty to an individual patient and protagonists of utilitarian arguments have to address hypothetical questions, such as 'Would you advocate antibiotic treatment to a febrile patient with acute tonsillitis who was a member of your family if, after you make your decision, you are to leave for a conference abroad where you are no longer in a position to monitor the situation personally?' Recent published opinions do not face up to these issues, giving the message that antibiotics work in selected cases but suggesting that they should not be used.

Similarly, if society wishes doctors to base decisions upon more utilitarian lines then doctors should be given unequivocal guidance and defended if harm to an individual ensued. For example, advice from the National Institute for Clinical Excellence advocated GPs should not prescribe the new anti-influenza drug Zanamivir but should still use their clinical judgement in an individual case.<sup>21</sup>

The current paper on UTIs<sup>6</sup> recognises the importance of NPTs in reducing antibiotic prescribing. However, bacterial culture is needed to monitor antibiotic resistance and also provides doctors with more reliable feedback. Perhaps doctors should be encouraged to use both NPTs and bacterial culture. With constant feedback they may be more able to identify patients in whom a 'wait and see' approach is reasonable, particularly those from whom previous samples in similar circumstances have not confirmed a UTI. For these women alternative diagnoses, such as chlamydial infection, should be considered. In general, a doctor's ability to estimate the prior probability of disease should improve with regular feedback. Conversely, there are arguments for not doing tests: Little<sup>9</sup> felt that, where resources are scarce, the cost of diagnostic tests is significant and evidence is lacking about their use. Sometimes even if NPTs are used, GPs may not change their prescribing decisions; for example, in only 13% of cases of patients with sore throats in one study.<sup>22</sup> It has been suggested that patient expectation of a diagnostic test might even encourage attendance.<sup>9</sup>

Hart considered that educating the public could encourage the prudent use of antibiotics and that there should be increased emphasis on infection and antibiotics in the undergraduate and postgraduate medical curricula, surveillance systems for antibiotic resistance, and the development and application of evidence-based guidelines on antibiotic use and prescribing.<sup>1</sup> The conclusions of Fenwick *et al.*,<sup>6</sup> showing antibiotic use to be the most cost-effective strategy in treating uncomplicated UTI in women, will come as no surprise to many GPs. Through years of experiential learning they are likely to have consciously or subconsciously worked out this decision analysis model for themselves.

We all wish to avoid the problems of antibiotic resistance caused by overprescribing of antibiotics and GPs should be ever more critical of their actions. Constant feedback from tests is important to complete learning cycles and enhance the diagnostic process. This is a prerequisite to effective evaluation of prescribing strategies, which could lead to antibiotics being prescribed only to the patients most likely to benefit.

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