Short communication

Ten-year mortality from Creutzfeldt–Jakob disease in Cyprus

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الوفيات الناجمة عن مرض كرتسفيلد جاكوب خلال عشر سنين في قبرص

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الخلاصة: يستعرض الباحثون في هذه الدراسة الوفيات الناجمة عن الحالات الفُرادية لمرض كرتسفيلد – جاكوب في قبرص خلال فترة عشر سنوات من الترصُّد (1995 – 2004). وقد تم خلال هذه الفترة اكتشافُ خمس حالات من بين 749 000 من السكان، مما يعطي معدل وقوع 0.7 حالة لكل مليون من السكان في العام. ويتماشى معدل الوقوع الذي وصل إليه الباحثون مع التوقعات التي أظهرها الترصُّد الوبائي العالمي. و لم يُعثر على أية ضروب من مرض كرتسفيلد – جاكوب، اللهم إلا حالة عائلية واحدة.

ABSTRACT We report the mortality from sporadic Creutzfeldt–Jakob disease in Cyprus for a 10-year surveillance period (1995–2004). In that time, 5 cases were identified out of a population of 749 000, giving an incidence of 0.7 cases per million population per year. Our sporadic incidence matches that expected according to global epidemiological surveillance. No cases of variant Creutzfeldt–Jakob disease were found but 1 familial case was diagnosed.

Surveillance sur dix ans de la mortalité due à la maladie de Creutzfeldt-Jakob à Chypre

RÉSUMÉ Nous présentons ici la mortalité imputable à la maladie de Creutzfeldt-Jakob sporadique à Chypre pendant une période de surveillance de dix ans (1995-2004). Au cours de cette période, 5 cas ont été recensés dans une population de 749 000 habitants, soit une incidence de 0,7 cas par million d'habitants et par an. Notre chiffre de l'incidence de la maladie sporadique correspond à celui auquel on pouvait s'attendre d'après la surveillance épidémiologique mondiale. Aucun cas de la variante de la maladie de Creutzfeldt-Jakob n'a été détecté, mais un cas familial a été diagnostiqué.

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Introduction

Creutzfeldt–Jakob disease (CJD) is a transmissible spongiform encephalopathy which occurs in distinct etiologic subtypes [*1*]. These include the sporadic form, which is the most common and occurs with an incidence of about 0.5–1.5 cases per million population per year, and constitute approximately 85% of all CJD cases [*2*]; iatrogenic forms that can be linked to contaminated surgical instruments or human tissue transplantation and, theoretically, blood products [*3*]; familial forms which are associated with mutations of the prion protein gene (*PRNP*) [*3*]; and variant CJD (vCJD) which was first identified in 1996 [*4*], which occurs predominantly in the United Kingdom [4] and has been linked to the bovine spongiform encephalopathy (BSE) epidemic [*5,6*]. In response to BSE, the British government, the European Union (EU) and the World Health Organization (WHO) recommended a number of measures including initiation of systematic surveillance of CJD and BSE [*7,8*]. Results from this collaborative EU surveillance on CJD have been published recently [*9*].

The Republic of Cyprus adopted the recommended measures including CJD surveillance in 1998. At that time, Cyprus was a candidate state for admission into the EU [*10*] and full EU membership was achieved in 2004. The population of the government-controlled area, for which surveillance data are available [*11*], was estimated at 749 000 at the end of 2004 and a case of sporadic CJD would be expected to be identified about every one and a half to two years. We report the incidence of CJD in the Cyprus for the 10-year period between 1995 to 2004. We have no available accurate and reliable data for the northern area of Cyprus which has been under Turkish occupation since 1974.

Methods

A surveillance system was set up, according to the WHO and EU directives [*8*], and suspected cases were referred to a surveillance centre where the first author acted as focal point. Diagnostic criteria formulated by the WHO and EU collaborative study were used [*8*]. Data collected between 1995 (the year for which records were available) and 2004 were analysed. The aim was to harmonize disease surveillance in accordance to EU practice, to collect accurate epidemiological data, and to monitor for the possible appearance of vCJD, especially in view of the fact that large numbers of British Cypriots relocated to Cyprus during the 1980s and 1990s [*11*]. Among them were many children and adolescents who would have lived in England during the BSE epidemic.

Determination of the presence of protein 14-3-3 in cerebrospinal fluid was carried out in all cases, either at the University of Gottingen, Germany or at the University of Edinburgh, Scotland. Magnetic resonance imaging and electroencephalograms (EEGs) were also obtained in all cases. Postmortem examination was performed in 2 cases. The patients were followed up closely until their death. Genetic analysis was obtained for a familial case. The mutational analysis for the familial case was performed at the Prion Unit at the National Hospital for Neurology and Neurosurgery in London.

Results

Two definite, 2 probable and 1 possible sporadic CJD cases were identified during the 10-year period. In addition, 1 familial case was diagnosed. No vCJD cases were found in Cyprus during the period of surveillance. Demographic and laboratory characteristics of the patients are shown on Table 1.

Table 1 **Characteristics of the patients with sporadic Creutzfeldt–Jakob disease**

Date of birth	Sex	Date of onset	Age at onset (years)	Date of death	Level of diagnosis[a]	Typical EEG	Protein 14-3-3	PrP analysis	Brain biopsy
09/09/35	F	April 1995	60	04/07/95	1	Yes	Positive	No	Yes[b]
25/05/26	M	October 1997	71	25/05/98	3	No	Negative	No	No
22/04/34	F	December 2000	65	05/02/01	1	Yes	Positive	Not known	Yes[b]
27/01/32	F	March 2003	69	20/05/03	2	Yes	Positive	No	No
01/02/44	M	February 2004	60	04/04/04	2	Yes	Positive	No	No

[a]1 = definite, 2 = probable, 3 = possible.
[b]Diagnostic of sporadic Creutzfeldt–Jakob disease.
EEG = electroencephalogram, F = female, M = male.

The first case died in July 1995, and the fifth in February 2004, with 3 other deaths in the interim; 3 cases were female and 2 male, one of which was the possible case. Age onset ranged from 60 to 79 years with an average age of 65 years. Duration of illness averaged 2.25 months for the definite/probable cases with a range of 2 to 3 months; the possible case lived for almost 8 months.

The familial case was alive at the time of this writing. He presented in January 1999 aged 45 years with a 4-year history of progressive forgetfulness, behavioural change and ataxia. His father had a similar illness and for the last 8 years of his life he was unable to stand. A paternal uncle was similarly affected. On examination there was nystagmus and truncal ataxia, and the Mini Mental Status Examination was 25/30. MRI showed generalized and cerebellar atrophy. Genetic testing of *PRNP* showed methionine homozygosity codon 129 and a novel insertional mutation. He has deteriorated gradually to the point that he is totally dependent on carers, severely dysarthric and dysphasic.

All definite/probable cases had typical EEGs characterized by periodic sharp and slow wave complexes. The EEG in the possible case was not typical showing diffuse slowing and disorganization. The EEG in the familial case showed semi-periodic triphasic waves.

All definite and probable cases were positive for protein 14-3-3. In the one case of possible sporadic CJD, protein 14-3-3 was negative.

Place of birth was also determined in order to establish whether any refugee cases had a common geographical origin. The 2 cases from Nicosia, in the centre of the island, were refugees and came from 2 villages (Kythrea and Lapithos), located in the north of the island. The remaining 3 originated and resided in non-occupied parts of Cyprus.

Occupationally, of the 3 females, 2 were housewives and the third a manual worker. Of the male cases, 1 was a carpenter and the other (possible case) was a lawyer. The familial case was a teacher.

No other significant factors or medical history were identified that would have increased the risk for CJD. None had received tissue transplants. None had thalassaemia major requiring transfusions of blood products. None had neurosurgical procedures.

Discussion

The adjusted incidence of CJD in Cyprus for the 10-year period of surveillance was

0.7 cases per million population per year. In other words, our sporadic incidence matched that expected [*12,13*] and there was no evidence for an increased risk of CJD in comparison to other countries. The clinical features were also as expected, except for a short average illness duration which may simply reflect the small number of cases identified.

Cyprus is an island of approximately 1000 square kilometres [*14*]. Following 1974, its 2 main communities were separated and since then the Greek-speaking population resides in the southern part whereas the Turkish-speaking population is in the northern part. The island's small size and the small number of cases detected does not allow meaningful clustering or statistical analysis. Another confounding factor is the issue of the aforementioned forceful separation of its 2 main communities in 1974; this has resulted in population shifts so that about 40% of the surveyed Greek population resides in parts of Cyprus other than their origin. Of our cases, 2 came from the city of Nicosia, 1 from Larnaca and 2 from Limassol. These are approximately equidistant from each other. The familial case also came from Limassol.

CJD surveillance appears to have worked fairly well for Cyprus. One important factor is the small size of the country, which allows adequate monitoring of the whole population in government-controlled areas of the country. Improved coordination is still needed, however, between the Ministry of Health, government and private neurologists, and neuropathologists, in order to ensure that most, if not all, cases receive a postmortem examination for a final, and definite, diagnosis. Of the 5 cases studied only 2 were examined neuropathologically even though the issue was discussed with all families. A possible factor for not obtaining permission for a postmortem may have been the perceived stigma, and one of the concerns of relatives after the diagnosis was made was the issue of confidentiality. In addition, a degree of reluctance was noted at times on the part on the pathologists, probably reflecting their own concerns about the transmissibility of CJD. Furthermore, genotypic analysis of *PRNR* should be carried out in order to identify genetic cases that might otherwise be labeled as sporadic. A recent Italian study showed that many genetic cases would have been classified as sporadic without mutation analysis [*15*]. The incidence of CJD in Cyprus is within the expected range and we believe that our cases were sporadic.

With Cyprus attaining full EU membership in 2004, the country has to follow certain decisions with regards to disease surveillance and epidemiology. This enables government to upgrade its policies and extend the investigations that are carried out in suspected CJD cases.

vCJD has not been identified in Cyprus. However, health authorities should remain vigilant with respect to this type of CJD as many Cypriots who used to live in England, a high-risk area for vCJD, moved back to the island after 1980.

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