SHORT COMMUNICATION

Transmissible spongioform encephalopathies (TSE) – prion diseases: their causes and risks

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Transmissible spongiform encephalopathies (TSE) – prion diseases represent a group of fatal, incurable and transmissible neurodegenerative diseases affecting humans and animals. They are at present the only known CNS disorders being both – genetically controlled and transmissible.

The main target of TSEs is CNS, where a disease specific, insoluble, partially protease resistent (PrPres, or PrPsc) glykoprotein – PRION – could be detected. Prion is a pathological isoform of the normal outer cellular membrane protein, expressed predominantly in the brain. This normal, protease sensitive, soluble form (PrPc or PrPsen) is transformed into abnormal prion in the diseased state. In humans prion protein is encoded in the prion gene (PRNP) on the chromosome 20.

The function of the cellular prion protein is not fully clarified. Experimental results demon-strate that it participates in the regulation of the sleep and normal cerebellar development and function. The sequence of prion amino acids and of normal cellular prion protein in the same individual is identical. The difference between the normal and pathological isoforms is only conformational. The specific diagnosis of prion diseases utilize the resistance of prion to proteases. When prion occurs in the examined tissue, it is not affected by proteinase K and could be detected by several laboratory methods.

The oldest (1738) known TSE is scrapie in sheep. Its direct transmission to man has never been proved. The indirect transmission of scrapie to humans could be considered according to the following hypothesis: cattle, mainly dairy cows were fed by meat and bone meal (MBM) produced from scrapie affected sheep. The technology of MBM production was altered in 1980‘s (reduced temperature, omission of detergents) what enabled the scrapie agent to sur-vive in the final product. A selection of the most resistant strain of scrapie during the passage in cattle resulted in a new disease – bovine spongiform encephalopathy (BSE).

Since 1920 to 1996 have been recognised 4 human TSEs: Creutzfeldt–Jakob disease (CJD), kuru, Gerstmann–Sträussler–Scheinker syndrom (GSS) and Fatal familial insomnia (FFI).

The most frequent and important human TSE is CJD. It appear to occur as sporadic, genetic and iatrogenic form.Sporadic cases are most frequent (85 %), they were found world-wide and their cause is still unknown. Genetic form represent about 10–15 % of all CJD cases. In these patients, CJD-specific mutation of PRNP gene could be detected. Iatrogenic form (1–5 %) has arisen following transplantation (cornea, dura mater), or treatment (human growth hormone, gonadotropin) of contaminated human tissue as well as by using contaminated neurosurgical instruments.

In 1996 – ten years after the outbreak of BSE epidemic – a new variant of CJD (vCJD) was described (6). The direct evidence (experimental transmission of the disease from animal to man) will never exist, however a growing number of indirect evidence (epidemiological, bio-chemical data and experimental transmission to transgenic animals) convincingly supports the causal relation between BSE and vCJD (1). How the disease was transmitted to man has not been clarified yet, but an increasing number of data support the per oral infection by food, containing either:

1. tissues with high titres of BSE agent (brain, spinal cord) in the past regularly added into minced products (burgers, sausages, pies and pake), or

2. contaminated tissues (e.g. muscles, contaminated by butcher’s instruments when processing brain or spinal cord, or mechanically recovered meat (MRM) occasionally with spinal cord remnants) (5, 7).

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This work was presented at the Meeting of the Slovak Medical Society which took place on May 7, 2001.

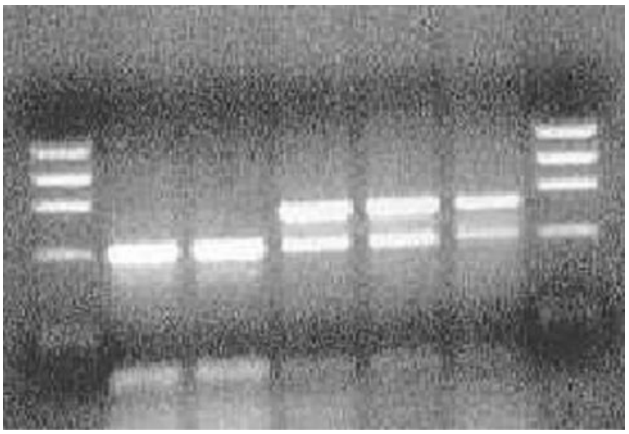

Fig. 1. Prion gene mutation (PRNP) "E200K"

The transmission of the disease to humans can be possibly better understood collecting data on clustering vCJD cases. It was reported that four out of 5 patients from the same locality regularly consumed bovine products manufactured by the same private butcher. To preserve the better taste, he wiped the meat (and brain) with towel cloths instead of washing it by water.

CJD surveillance in Slovakia started in 1975, when the first definitive case of CJD was diagnosed and the disease was successfully transmitted to domestic cats. The first case of scrapie in sheep was histopatologically confirmed in Slovakia in 1987 and the first laboratory evidence of scrapie, verified by specific diagnostic methods, was done in 1991.

CJD in Slovakia is characterised by certain specific features. The total number of definitive CJD cases, all classical variant, are 141. The diagnosis was confirmed histopathologi-cally, since 1990 also by other (SAF, molecular biology, immunohistochemistry, Western blot) specific methods. Iatrogenic CJD was not yet detected (2). Comparing to world wide occurrence, in Slovak CJD group only 25 % of patients are sporadic and as much as 75 % are genetic cases. All notified genetic patients have CJD-specific mutation of the PRNP gene on the codon 200 (E200K mutation). 36.4 % of healthy relatives of genetic CJD cases carried the same E200K mutation (Fig. 1). These asymptomatic carriers represent a "genetic CJD-risk group" in Slovak population. Despite of numerous marriages recorded between relatives, the mutation was found only on one allele, always in that with methionine on codon 129 of the PRNP gene. The causal relation of E200K mutation to CJD was demonstrated and proved in Slovak CJD group. The penetrance of the E200K mutation in Slovak carriers is 62.85 % (4).

The mutation E200K is the most frequent and widely spread human TSE-specific mutation. Besides of Slovakia, E200K carriers are frequent in Lybian Jews in Israel, in citizens of Slovak origin in Hungary and in Chile. They were found also in Italy, France, Germany, Austria and Japan. The mutation was detected in CJD – affected Slovak immigrants to USA, Canada, France and Belgium.

Besides of the confirmed endogenous, genetic CJD-risk a further, remarkable finding was provided by the analysis of exogenous risk factors. The professional distribution of patients suggested a possible CJD risk in health-professionals and farm workers. Epidemiological and genetic analyses excluded the professional risk in health workers (3). A significant difference of the farm workers in general Slovak population (7 %) comparing to CJD group (51 %) has not yet been satisfactorily explained.

The occurrence of vCJD has not been proven yet in Slovakia. The 29 years old, suspect vCJD patient has been working for more than a year in Italy. Clinical course and laboratory investigation suggested vCJD, but since an autopsy was not carried out, the case could never be definitively concluded.

Preventive measures against iatrogenic CJD and vCJD are focused on the following:

1. Control of the imported, potentially contaminated food, cosmetic and drugs. Regarding the large – scale export of cattle commodities with a possible BSE risk from UK to certain EU countries during the critical period (France, Germany), the difference in the risk degree con-cerning the import from UK and these countries is almost negligible.

2. Prevention of the iatrogenic CJD due to invasive interventions and increasing number of transplantations. TSE-specific mutations indicate a contraindication for tissue and organ donation. Because of proven genetic CJD – risk group in Slovakia, one of such measures is focused on genetic testing of all corneal donors for E200K mutation. The justification of such a testing was documented by evidence of 2 E200K carriers in the group of 541 tested donors.

In the past was Slovakia the first country where obligatory reporting of suspect CJD cases was introduced (1979). At present it is the first state with a systematic genetic examination of corneal donors in order to exclude carriers of E200K mutation from the list of potential corneal donors and to prevent iatrogenic CJD.

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Received June 7, 2003.
Accepted October 27, 2003.