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Molecular subtype-specific clinical diagnosis of prion diseases

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Abstract

Sporadic Creutzfeldt–Jakob disease (sCJD) is a rare transmissible disease caused by accumulation of pathological prion protein (PrP^{sc}) in the CNS. According to the codon 129 polymorphism (methionine or valine) and the prion protein type 1 or 2, a classification into distinct subtypes was established. Further analysis of these subtypes detected atypical clinical forms with longer disease duration or younger age at onset.

The CJD subtype influences sensitivity of the technical investigations such as 14-3-3 in CSF, periodic sharp wave complexes in the EEG or hyperintense basal ganglia in MRI. A further characterization of these subtypes is important for reliable diagnosis and identification of rare disease variants. The aim is to establish specific patterns of test results and clinical findings. These improvements in diagnostics may be the reason for the apparent increase in sCJD incidence in Germany from 0.9 in 1994 to 1.6 in a million in 2005. Despite careful surveillance, no patient with variant CJD has been detected to date in Germany.

Here we present the data of the CJD surveillance of the last 13 years. Additionally, the improvements in diagnostics and differential diagnosis are discussed.

Keywords: Dementia; CJD; Subtype; 14-3-3; Transthyretin; MRI

1. Introduction

Creutzfeldt–Jakob disease (CJD) is a rapid progressive disorder characterized by dementia associated with cerebellar signs, visual disturbances, extrapyramidal/pyramidal signs, myoclonus and akinetic mutism in the final disease stages (Zerr and Poser, 2002). Clinical diagnosis is supported by periodic sharp wave complexes (PSWC) in EEG and 14-3-3 detection (a neuronal protein, which is used as a surrogate marker of rapid neuronal destruction) in CSF. Additionally, MRI findings such as hyperintensities of basal ganglia, thalamus or cortex are often detected, but the pathogenetic correlate is still not known (Kallenberg et al., 2006). A new potential CSF marker for dementia is transthyretin (TTR), a carrier of the thyroid hormone thyroxine. TTR levels are known to be lower in CSF in patients suffering

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from Alzheimer's disease (AD) (Castano et al., 2006).

CJD is caused by accumulation of the β-sheet rich, pathological PrP^{sc} after conversion of the alpha-helical, physiological PrP^{c}. Most patients (around 85%) suffer from the sporadic form of CJD (sCJD). Also, mutations of the prion protein gene (*PRNP*) on chromosome 20 can destabilize the protein conformation and thus enhance conversion of PrP^{c} to PrP^{sc}. A lot of mutations have been described so far with point mutations and inserts (Kovacs et al., 2005) occurring. The clinical spectrum of genetic prion diseases is wide and such separate entities as fatal familial insomnia (FFI) and Gerstmann–Straeussler–Scheinker syndrome (GSS) have been defined. As prion diseases are also infectious, acquired forms are known. Iatrogenic transmission can be caused by dura mater grafts, cadaveric human growth hormone, neurosurgical procedures or the use of deep brain electrodes (Will, 2003). In 1996, a new variant of CJD (vCJD) was described in the UK, and a causal link to uptake of BSE- (bovine spongiform encephalopathy) contaminated food was shown (Will et al., 1996).

Polymorphism at codon 129 of the prion protein gene (*PRNP*) with either methionine (M) or valine (V) is known to alter susceptibility (MM is a risk factor for sCJD), incubation time and phenotype of the disease. In combination with PrP^{sc} type 1 or 2, there were defined six subtypes with different clinical and neuropathological characteristics (Parchi et al., 1996, 1999).

The different forms of CJD in humans, with variable clinical syndromes and origins, make surveillance and detection of the disease particularly difficult. Thus, a detailed knowledge of the subtype-specific clinical spectrum and findings in CSF, EEG and MRI is essential. Here, we characterize subtype-specific findings and describe the resulting data of the German CJD Surveillance of the last 13 years.

2. Patients and methods

2.1. Surveillance

The surveillance of Creutzfeldt–Jakob disease in Germany has been performed prospectively since 1993. The patients were reported by the treating physicians to the specialized Unit in Göttingen, and examined by a study physician in the notifying hospital. CSF samples for 14-3-3 analysis as well as copies of EEG and MRI were obtained. Blood samples for full sequencing of the prion protein gene (*PRNP*) and codon 129 analysis completed the dataset. Clinical diagnosis was performed according to the established criteria as probable or possible CJD or other diagnoses (WHO, 1998; Zerr et al., 2000). Autopsy for confirmation of the clinical diagnosis by immunohistochemistry and histological parameters were sought. Prion protein type 1 or 2 was determined as described previously (Parchi et al., 1996).

2.2. CSF analysis

CSF samples of the patients were collected for each patient included in the surveillance, also during the course of the surveillance period. The samples were stored at −80 °C. 14-3-3 were measured by Western blot with the K19 antibody (Santa Cruz) by standard methods and evaluated qualitatively as positive or negative (Zerr et al., 1998). Total tau (Innotest AG, Eschlikon, Switzerland) and β-amyloid (Genetics) were measured quantitatively by ELISA as described in the literature (Sunderland et al., 2003). Transthyretin was measured by nephelometry (N Antiserum to Human Albumin, Prealbumin and Retinol-binding protein®; Dade Behring, Marburg, Germany).

2.3. MRI analysis

MR scans were collected during surveillance at the reporting hospitals. Scans of FLAIR, T2 and DWI were evaluated for CJD typical findings, while in other weightings no CJD typical findings are described. Evaluation was performed according to a standardized protocol for hyperintensities in six different cortical regions, four parts of the basal ganglia and three thalamic nuclei.

3. Results

3.1. Epidemiology

During the 13 years of surveillance (1993–2006), we identified 1332 patients with sporadic CJD (696 confirmed, 636 probable). Autopsies were performed