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Abstract

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Total Prion Protein Levels in the Cerebrospinal Fluid are Reduced in Patients with Various Neurological Disorders

Felix Meyne, Sara Friederike Gloeckner, Barbara Ciesielczyk, Uta Heinemann, Anna Krasnianski, Bettina Meissner and Inga Zerr *

National TSE Reference Center at Department of Neurology, Georg-August University, Göttingen, Germany

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Abstract. We performed a study on levels of the total prion protein (PrP) in humans affected by different neurological diseases and assessed the influence of several factors such as age, gender, and disease severity on the cerebrospinal fluid PrP levels. PrP-ELISA technique was used to analyze cerebrospinal fluid (CSF) samples. 293 CSF samples of patients with Creutzfeldt-Jakob disease (CJD), Alzheimer’s disease, dementia with Lewy-bodies, Parkinson’s disease, multiple sclerosis, cerebral ischemia, generalized epileptic seizures, and meningitis and encephalitis in comparison to controls were analyzed. We found a significant reduction of CSF PrP levels in patients suffering from all neurodegenerative disorders analyzed. This group exhibited mean PrP values of 164 ng/ml while non-neurodegenerative disorder patients and healthy controls showed PrP levels of 208 ng/ml and 226 ng/ml, respectively. CSF levels correlated with disease severity in CJD, Alzheimer’s disease, and dementia with Lewy-bodies. The finding of decreased PrP levels in the CSF of patients not only with CJD but also in other neurodegenerative disorders is intriguing. Age-, gender-, and genetic-specific factors might be involved in the PrP c regulation.

Keywords: Alzheimer’s disease, amyloid-β, cerebrospinal fluid, Creutzfeldt-Jakob disease, dementia, dementia with Lewy-bodies, disease severity, prion protein, tau

INTRODUCTION

The physiological prion protein (PrP c) is an evolutionarily highly conserved protein [1,2], which is encoded in all mammals investigated. PrP c is attached to the outer surface of the cell membrane by a GPI-anchor [3]. PrP c is mainly expressed in neurons but also in other cell types such as blood cells. A posttranscriptional conversion of the physiological PrP c leads to the pathologic isoform PrPSc, which is a key event in the pathogenesis of transmissible spongiform encephalopathies (TSE) in humans and animals. PrPSc accumulates during these diseases in neural and other tissues [4–6].

The functional role of the physiological PrP c is still not fully understood. Recent studies have shown that PrP c is a copper-binding protein with antioxidant properties [7–10]. These antioxidant properties are based on a superoxide dismutase-like activity in the octapeptide-region of the protein and seem to be involved in its neuroprotective properties by reduction of oxidative stress. Additionally, it has been shown that neuroprotection is triggered by inhibition of Bax-mediated neuronal apoptosis [11] and that PrP c is involved in the activation of several signal transduction pathways playing an important role in neuronal survival [12–15]. Recently, Parkin and colleagues demonstrated that cellular overexpression of PrP c inhibits the β-secretase cleavage of the amyloid-β protein precursor (AβPP) and reduces amyloid-β (Aβ) formation [16].

Since knowledge regarding regulation of PrP c in humans is limited, we analyzed the total PrP levels in...
the cerebrospinal fluid (CSF) of patients with various neurological diseases. This approach was chosen since the composition of proteins in the CSF is assumed to reflect pathological processes in the brain. We used CSF samples from patients with various neurodegenerative diseases such as Creutzfeld-Jakob disease (CJD), Alzheimer’s disease (AD), dementia with Lewy-bodies (DLB), Parkinson’s disease (PD), and also non-degenerative diseases such as epileptic seizures, meningitis and encephalitis, multiple sclerosis (MS), and cerebral ischemia in comparison to controls without any organic diseases of the central nervous system.

Special focus was given to the influence of the disease course, age and gender, and the \( \text{PRNP} \) M129V polymorphism in CJD patients on PrP levels and to the question of whether PrP can function as a diagnostic biomarker, similar to commonly used biomarkers like \( \text{A}^{\beta}_{1-42} \) and tau protein in dementia diagnosis.

METHODS

Cerebrospinal fluid samples

CSF samples were collected in the Neurochemistry Laboratory at the Department of Neurology, Georg-August University, Goettingen between January 1997 and December 2005. The patients received inpatient or outpatient treatment at the Department of Neurology and were given a lumbar puncture during diagnostic procedure. Additionally, CSF samples were sent from referring German hospitals to the National TSE Reference Center at the Department of Neurology in order to determine 14-3-3 proteins for a differential diagnosis of CJD. Only CSF samples which were centrifuged and immediately frozen after collection and stored at \(-80^\circ\text{C}\) until processing were used in this study. Blood contaminated samples were excluded from analysis. Informed consent was available for all patients.

Patients

Controls: These patients had lumbar punctures with normal CSF findings. An organic disease of the central nervous system was excluded during the diagnostic workup. Diagnoses in this group of patients were mainly depression, polyneuropathy, vertigo, or pain syndromes.

Creutzfeld-Jakob disease: All individuals in this group were deceased and postmortem neuropathological examination confirmed the diagnosis, when performed. Only definite or clinically probable sporadic (after exclusion of \( \text{PRNP} \) mutation) cases were included in the analyses. Codon 129 genotype (rs1799990) was determined as described elsewhere [17].

Alzheimer’s disease: The diagnosis in these patients based on the NINCDS-ARDA criteria [18].

Dementia with Lewy-bodies: The diagnosis was based on criteria of the consensus conference of 1996 [19].

Parkinson’s disease: The diagnosis was based on criteria of ICD-10 [20].

Epileptic seizures: We analyzed the CSF of patients with generalized epileptic seizures. The mean time of lumbar puncture was at day \(3 \pm 2\). Patients with symptomatic seizures such as space occupying lesions or encephalitis were excluded.

Cerebral ischemia: Cerebral ischemia was confirmed by brain imaging analyses (either computed tomography or magnetic resonance imaging). The mean time of lumbar puncture was \(7 \pm 4\) after the ischemia-event.

Multiple sclerosis: This group was heterogeneous, including patients with primary progressive and relapsing forms. The lumbar puncture was performed at the time of initial diagnosis for clinical workup. McDonald criteria were used for the diagnoses [21].

Meningitis/encephalitis: The diagnosis was based on ICD-10 [20]. This group consisted of meningitis and encephalitis affected by various bacterial and viral pathogens.

The number of patients in each group and age and gender distribution is given in Table 1.

PrP ELISA

We used Platelia® BSE-Detection Kit (BIO-RAD Laboratories GmbH, Munich, Germany) according to the manufacturer’s instructions. This kit is based on ELISA techniques and is employed as a rapid BSE test for qualitative determination of PrP\(^{\text{Sc}}\) in the brain stem tissue of cattle and sheep. For our experiments, we omitted the Proteinase K digestion step, which digests PrP\(^\text{c}\), but not PrP\(^{\text{Sc}}\), since our aim was to determine total PrP levels in the CSF (in subjects with prion diseases PrP\(^\text{c}\) plus potentially extremely low amount of PrP\(^{\text{Sc}}\)) [22]. CSF samples were applied undiluted. Calibration was performed with recombinant PrP (Prionics, Zurich, Switzerland) and a calibration curve was calculated. This curve was used to determine the PrP concentrations based on the values obtained from the ELISA assay. The signal was measured at 450 nm with a 1420 Multilabel Counter Victor 2 (Wallac).
Table 1: Core clinical data and PrP results

<table>
<thead>
<tr>
<th>Neurodegenerative diseases</th>
<th>All, n (M/F)</th>
<th>Age, median ± SD</th>
<th>PrP&lt;sub&gt;c&lt;/sub&gt; ng/ml mean ± SD</th>
<th>PrP&lt;sub&gt;c&lt;/sub&gt; ng/ml mean ± SD</th>
<th>PrP&lt;sub&gt;c&lt;/sub&gt; ng/ml mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>male</td>
<td>female</td>
<td>all</td>
</tr>
<tr>
<td>CJD</td>
<td>117 (48/69)</td>
<td>64 ± 11</td>
<td>62 ± 9</td>
<td>66 ± 11</td>
<td>160 ± 76</td>
</tr>
<tr>
<td>AD</td>
<td>29 (11/18)</td>
<td>64 ± 10</td>
<td>62 ± 11</td>
<td>65 ± 10</td>
<td>177 ± 80</td>
</tr>
<tr>
<td>DLB</td>
<td>21 (13/8)</td>
<td>76 ± 7</td>
<td>75 ± 6</td>
<td>77 ± 8</td>
<td>162 ± 66</td>
</tr>
<tr>
<td>PD</td>
<td>27 (12/9)</td>
<td>70 ± 9</td>
<td>72 ± 7</td>
<td>66 ± 12</td>
<td>174 ± 81</td>
</tr>
<tr>
<td>Ischemia</td>
<td>21 (12/9)</td>
<td>64 ± 13</td>
<td>64 ± 10</td>
<td>63 ± 17</td>
<td>193 ± 77</td>
</tr>
<tr>
<td>MS</td>
<td>11 (4/7)</td>
<td>44 ± 12</td>
<td>48 ± 8</td>
<td>41 ± 14</td>
<td>226 ± 49</td>
</tr>
<tr>
<td>Meningitis &amp; encephalitis</td>
<td>14 (9/5)</td>
<td>48 ± 23</td>
<td>50 ± 25</td>
<td>46 ± 20</td>
<td>222 ± 82</td>
</tr>
<tr>
<td>Epileptic seizures</td>
<td>13 (8/5)</td>
<td>33 ± 18</td>
<td>41 ± 21</td>
<td>28 ± 15</td>
<td>201 ± 63</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>40 (18/22)</td>
<td>49 ± 19</td>
<td>53 ± 19</td>
<td>45 ± 18</td>
<td>226 ± 79</td>
</tr>
<tr>
<td>&gt;40y</td>
<td>24 (13/11)</td>
<td>62 ± 12</td>
<td>63 ± 12</td>
<td>60 ± 12</td>
<td>262 ± 70</td>
</tr>
<tr>
<td>&lt;40y</td>
<td>16 (5/11)</td>
<td>30 ± 7</td>
<td>29 ± 9</td>
<td>30 ± 6</td>
<td>185 ± 48</td>
</tr>
</tbody>
</table>

Aβ<sub>1–42</sub> ELISA

Aβ<sub>1–42</sub> levels were determined by using the hAmyloid β<sub>12</sub> ELISA kit (Genetics company, Schlieren, Switzerland, lowest detection limit 100 pg/ml).

Tau

Tau protein levels were determined by using ELISA-techniques (INNOTEST® hTau Ag; Innogenetics, Ghent, Belgium, lowest detection limit 60 pg/ml).

Statistics

The statistical evaluation was done with SPSS for Windows (11.5). One-way ANOVA followed by Bonferroni-test was used to analyze the data. For single-pair wise comparison (detection of gender differences), the Mann-Whitney U test was used.

Correlation analyses of PrP and one potentially influencing variable (e.g., age in controls) were performed by linear regression analyses. For more than one potentially influencing variable on PrP levels (e.g., disease severity, genotype, and age), stepwise multiple linear regression analyses were used to assess the influence of a single parameter (all results were given as beta coefficients). For these analyses, PrP was used as criterion variable and considered (predictor) variables were given in parentheses. All values were shown as means ± standard deviation (SD). Values of p < 0.05 were considered to be significant.

For graphical presentation of the statistical analyses, we used the BOX-and Whisker-Plot. In order to evaluate the diagnostic value of PrP, we determined the optimal cut-off point, which gives the best balanced sensitivity and specificity ratio [Youden-Index (sensitivity + specificity-1 = Youden)].

Criteria for severity of dementia in AD and DLB patients

To investigate the influence of disease course on PrP levels, we stratified the data in three groups of severity codes. These divisions were made on the basis of the Mini-Mental Status Examination (MMSE) or, if this test was not available, on clinical criteria.

State 1: Minimal cognitive impairment (MMSE 24–29 points) or mild dementia (MMSE 20–23 points); Clinical criteria – not disoriented or possibly mild disoriented regarding time.

State 2: Moderate dementia (MMSE 10–19 points); Clinical criteria – moderate disoriented regarding time and/or place, not disoriented regarding situation and person.

State 3: Severe dementia (MMSE 0–9 points); Clinical criteria – severe disoriented regarding time, place and situation, possibly disoriented regarding person.

Criteria for disease severity in CJD patients

We divided the time of lumbar puncture to disease onset in each patient by the total duration of the disease. Thus, we classified patients in three categories according to whether they underwent lumbar puncture in the first (time of lumbar puncture to disease onset/total duration time).
RESULTS

PrP levels in the CSF

Table 1 displays the mean CSF levels of PrP in our patients. The data for controls were stratified by age 40 and two groups were analyzed (controls younger than 40 at lumbar puncture, “younger controls”, and controls older than 40 at lumbar puncture, “older controls”) (Table 1). Because of a potential influence of age on PrP levels, the values in special patient groups were first compared to the whole control group and then to older or younger control patients, respectively.

Neurodegenerative diseases (CJD, AD, DLB, and PD) had mean PrP levels of 164 ng/ml CSF. They were significantly lower in comparison to the whole group of controls ($p < 0.001$) and to the whole group of non-neurodegenerative diseases ($p < 0.001$). For the group of controls, we determined mean PrP levels of 226 ng/ml (Table 1). Comparing each neurodegenerative disease with the older control group, we found significantly reduced PrP CSF levels ($p < 0.001$ for CJD, DLB, and PD and $p = 0.001$ for AD) (Fig. 1). No differences were observed between CJD, AD, DLB, and PD. Non-neurodegenerative/non-vascular diseases (MS, meningitis and encephalitis, epileptic seizures) had mean PrP levels of 216 ng/ml (Table 1). No differences were seen between MS and meningitis/encephalitis compared to older as well as younger control patients. Additionally, we could not find differences between CSF PrP levels in epileptic seizure patients (this group consisted of young individuals) in comparison to younger controls.

Finally, patients with cerebral ischemia had mean PrP levels of 193 ng/ml (Table 1). Although some individuals in this group were characterized by low PrP levels, statistical significant differences in PrP levels could not be confirmed when compared to the older controls.

Influence of age and gender

A positive relationship between age and PrP levels was observed in the control group ($p = 0.01; \beta = 0.40$) (Fig. 2a and b). These results were mainly caused by
The values of female controls ($p = 0.001; \beta = 0.64$) (see Fig. 2b), since no correlation was seen between age and PrP in male controls ($p = 0.50; \beta = 0.17$) (see Fig. 2a). The correlation between age and PrP levels in all other disease groups revealed no significant results. However, significant results and trends toward significant results could be detected in combined groups such as all neurodegenerative groups ($\beta = 0.16; p = 0.03$) (age; disease severity) and all non-neurodegenerative groups ($\beta = 0.302; p = 0.065$). In contrast to the control group, the impact of gender in the disease groups was balanced.

With exception to our younger control group ($p = 0.008$), PrP levels did not differ significantly between males and females.

**Influence of severity codes of dementias and disease duration**

The stratification of the data by severity codes revealed lower PrP levels in patients with advanced disease stages in the group of neurodegenerative disorders (CJD, AD, DLB; Fig. 3a,b,d,e). Levels of PrP in severe and moderate state of dementia in comparison to older controls and in mild state in comparison to severe state of dementia were statistically significant ($p < 0.05$).

These results were mainly striking in AD and CJD patients, but low PrP levels in advanced disease states were also detectable in patients with DLB.

**Influence of codon 129 genotype on PrP levels in CJD**

The polymorphism at codon 129 was determined in a total of 107 CJD patients. 67% ($n = 72$ patients) were homozygous for methionine (MM), 18% ($n = 19$ patients) were heterozygous for methionine and valine (MV), and the remaining 15% ($n = 16$ patients) were homozygous for valine (VV). MM patients had mean PrP CSF concentrations of 167 ng/ml, MV patients had mean CSF values of 139 ng/ml, and VV homozygous patients had a mean CSF value of 140 ng/ml. Our results revealed significantly lower PrP concentrations in the CSF of male patients with valine at codon 129 ($\beta = -0.31; p = 0.05$) (genotype, age, disease severity). For female CJD patients, no influence of the genotype was observed ($\beta = 0.03; p = 0.79$) (genotype, age, disease severity) (Fig. 3c).

**Diagnostic value of PrP**

We investigated whether PrP levels in the CSF might be used as a potential diagnostic biomarker in dementia or PD. PrP levels lower than 200 ng/ml were found in 72% for the whole dementia group (CJD, AD, DLB, PD) with a specificity of 88% when healthy controls were used to calculate this parameter. Using the cut-off, which gives the best Youden-Index, PrP levels were decreased in 76% of CJD, 72% of AD, 76% of DLB, and in 63% of PD samples (Table 2).
a) Combined neurodegenerative groups (CJD, AD, and DLB)

b) Influence of disease severity in CJD

c) CJD and codon 129 genotype

d) Influence of disease severity in AD

e) Influence of disease severity in DLB

Fig. 3. Influence of disease severity on mean PrP levels.
Correlation of PrP and other biomarkers

Next, we analyzed a potential correlation between PrP and both commonly used biomarkers for dementia in the CSF:

Aβ1-42 values were determined in 76 samples of CJD (mean levels 544 ± 359 pg/ml), 18 samples of AD (mean levels 323 ± 137 pg/ml), and 8 samples of DLB (mean levels 110 ± 36 pg/ml).

Tau values were determined in 112 samples of CJD (mean levels 8624 ± 7252 pg/ml), 18 samples of AD (mean levels 415 ± 445 pg/ml), and 12 samples of DLB (mean levels 310 ± 107 pg/ml).

We found a significant positive correlation between PrP and Aβ1-42 in the group of neurodegenerative diseases (β = 0.25; p = 0.007), which was most apparent in CJD (β = 0.46; p = 0.001) and AD patients (β = 0.63; p = 0.005) (Fig. 4a, 4c). In the subgroup of DLB (β = 0.46; p = 0.25) (Fig. 4e), the correlation between these markers was not significant.

The correlation of tau levels with PrP for the whole group of neurodegenerative diseases did not reveal significant results (β = 0.07; p = 0.39), but in AD (β = 0.65; p = 0.003) and DLB patients (p = 0.006; β = 0.74), significant correlations could be detected (Fig. 4d, 4f). In CJD (Fig. 4b), no correlation was observed (β = 0.11; p = 0.26 and β = 0.23; p = 0.480).

PrP levels were correlated with a semiquantitative 14-3-3 Western blot analysis (grade 0 = not detectable, 1 = weak band, 2 = intermediate band, and 3 = strong band). There was a non-significant positive correlation of PrP and 14-3-3 levels in CJD patients (β = −0.219, p = 0.07). When we stratified the data by gender, the correlation became significant for men (β = −0.504, p = 0.014), but not for women (β = −0.0904, p = 0.535).

DISCUSSION

In this study, we investigated the CSF PrP levels in patients with various neurological disorders such as CJD, AD, DLB, PD, encephalitis and meningitis, cerebral ischemia, MS, and epileptic seizures in comparison to controls. Our results revealed a significant decrease of PrP CSF levels in neurodegenerative disorders versus non-neurodegenerative diseases and controls. The decrease of PrP was greater in severe demented AD patients than in patients with mild or moderate disease. This was also observed in CJD; patients in advanced disease stages had lower PrP values than patients at early stages. The reasons for this are not fully understood, since almost no study has reported on the role of PrP in humans so far. Since we could only observe the decrease of PrP levels in neurodegenerative disorders and since this decrease is clearly correlated to disease severity, our results might simply reflect brain atrophy in these diseases, but might also be related to some other common mechanisms. The state-dependent decrease of PrP CSF levels was observed in all neurodegenerative conditions analyzed here with exception of DLB. However, only a few patients with early DLB were analyzed, which might be explained by the difficulty in diagnosing DLB at very early stages. The low number of mild and moderate demented patients in DLB could be the reason that we did not observe clear correlations but only a trend towards low levels at advanced disease stages.

The study was motivated by recent findings of PrP in AD. Codon 129 homozygosity is a well-known risk factor for CJD [23] and was demonstrated recently to be a risk factor in other dementia as well. Codon 129 homozygosity for methionine is associated with AD [24] and for valine with a risk of cognitive decline [25,26]. A study has demonstrated that AD brains are characterized by an increase of intraneuronal PrP immunoreactivity compared to controls [27]. It remains unknown, however, if the increased PrP signals are the consequence of an oxidative stress-induced upregulation of PrP. Another hypothesis is that increased immunoreactivity is due to a decelerated degradation of PrP. Furthermore, a block in intracellular trafficking of PrP to the cell surface could also be responsible for the increased immunoreactivity [27]. Another exciting piece of work was done by demonstrating that cellular over-
expression of PrPc inhibits the β-secretase cleavage of AβPP and reduces Aβ formation [16] and that characteristics of PrP isoforms in some AD brains might differ from controls [28].

Aβ and PrPc are co-localized in senile plaques in AD as well as in Lewy bodies in PD [29]. For AD, the
accumulation of proteins such as Aβ plays a key role in pathogenesis. The deposition of Aβ was discussed to be the reason for decreased Aβ values in the CSF in patients with AD [30]. Whether the reduction of PrP in CSF of patients with AD and other neurodegenerative disorders is linked to the deposition by similar mechanisms in the brain tissue remains to be determined.

The finding of a positive correlation of total PrP and total tau levels in AD is intriguing. First, we have found a decrease in PrP levels with dementia severity in AD. One would expect an increase in total tau levels with dementia severity in AD and thus a negative correlation on PrP and tau. However, there is no clear evidence that tau levels increase during AD. In fact, most longitudinal studies on tau levels in AD failed to show such a correlation [31–33]. Studies on dementia severity and biomarkers point toward a correlation between high tau levels and clinical dementia rating scores, but data are limited and further studies on this subject are needed [32].

We were also interested in the proportion of decreased PrP levels in various conditions with respect to the usefulness as a potential biomarker. PrP levels were decreased in all neurodegenerative diseases studied here; thus, similar to other currently available biomarkers such as Aβ and tau, it does not discriminate between single conditions [34].

We analyzed several factors which might alter PrP levels, such as age, gender, and codon 129 genotype. PrP values in valine homozygous male patients were determined to be lower than in MV and MM patients; however, for female VV patients, these results could not be demonstrated. One potential factor, which should be analyzed in future studies, is the effect of longer disease duration, which was repeatedly described in valine homozygous CJD patients [35,36].

Age and gender seem to influence PrP expression or turn-over. An age-correlated PrP expression was found in human peripheral blood leukocytes [37]. Additionally, Williams and colleagues found age-related increase in PrP in cerebral microvessels and in microvessel-depleted brain homogenate in mice [38]. To our knowledge, there are no studies that found an influence of gender on PrP levels. In our study, we found a correlation of age and PrP levels in controls and in combined groups of neurodegenerative disorders. In controls, this correlation was based on increasing PrP levels with age in female controls. However, the low number of healthy controls included in this study is a limitation and the results of stratified tests, like age and gender correlations, should be taken with caution.

In the present study, we have found differences between PrP levels in neurodegenerative conditions and aged controls. While we speculate that PrP levels are reduced in neurodegenerative conditions, we cannot entirely exclude that levels in old controls are abnormally increased. However, since our control group was comprised of patients with non-organic disorders and peripheral (not central nervous system-related) conditions, this hypothesis seems unlikely.

In conclusion, we report the first data on PrP in CSF in humans with various neurological disorders. PrP levels in the CSF were significantly reduced in patients suffering from CJD, DLB, PD, and AD in comparison to patients suffering from non-neurodegenerative diseases and to healthy controls. Further work needs to be done to clarify the role of PrP alterations in neurodegeneration, but also to identify potential biochemical and structural PrP alterations in various conditions.

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