Influence of $BDNF$ polymorphisms on Wilson’s disease susceptibility and clinical course

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Abstract Susceptibility to Wilson’s disease (WD) and its clinical manifestations are thought to be affected by genetic factors, including polymorphisms. The role of brain-derived neurotrophic factor ($BDNF$) in the pathogenesis of neurodegenerative diseases is now widely discussed. The aim of the present study was to evaluate the frequency of the $BDNF$ Val66Met (G-196A) and C-270T polymorphisms in WD patients and in healthy controls, and to determine the role of these polymorphisms in the clinical characteristics of WD. We found that the $BDNF$ Val/Val (−196 G/G) and −270 C/T genotypes occurred more frequently in WD patients than in healthy controls (66 % versus 45.5 %, $p = 0.0001$, and 14 % versus 6 %, $p = 0.018$, respectively). Similarly, symptomatic patients carried the $BDNF$ Val/Val genotype more often than presymptomatic patients (75 % versus 53 %, $p = 0.0097$). No association was detected between any of the determined polymorphisms and the dominant form of the disease or the age of onset for WD.

Keywords Brain-derived neurotrophic factor ($BDNF$) · Polymorphism · Wilson’s disease · Disease susceptibility

Introduction

Wilson’s disease (WD) is a rare inherited disease of copper metabolism that can lead to the accumulation of copper and damage to several organs. The main symptoms are liver failure and neuropsychiatric manifestations; symptomatology and age at symptom onset are thought to vary greatly among patients. Genetic variability, including gene mutations and polymorphisms, may underlie this variability. Mutation of $ATP7B$ has been shown to affect disease manifestation (Gromadzka et al. 2006), but polymorphisms in, for example, the methylytetrahydrofolate reductase gene (Gromadzka et al. 2011), some cytokine genes (Gromadzka et al. 2011), and the apolipoprotein gene (Schierfermeier et al. 2000; Litwin et al. 2012) may be essential for the clinical characteristics of WD. Other genes, such as those encoding antioxidant-1, copper metabolism gene MURR1 domain-containing protein, and X-linked inhibitor of apoptosis have also been investigated, but with conflicting results (reviewed by Litwin et al. 2013).

Although WD is recognized as a neurodegenerative disease, previous studies of the pathogenesis of some neurodegenerative disorders revealed increased expression of proinflammatory cytokines in the brains of experimental animals and of patients. The inflammatory process is considered to be one step in neuronal degeneration (Frank-Cannon et al. 2009). The role of neurotrophins, including polymorphisms in brain-derived neurotrophic factor ($BDNF$), is now discussed widely with regard to susceptibility to neurodegeneration and to the courses of various neurological diseases, such as Parkinson’s disease (Gao et al. 2010), Alzheimer’s disease (Laske et al. 2006), and Huntington’s disease (Albrech et al. 2005; Koshikawa et al. 2006). The effects of polymorphisms have also been explored in multiple sclerosis (Mirowska-Guzel et al. 2008; Mero et al. 2012), a disease in which neurodegeneration is thought to be secondary to autoimmunity.

The best-known $BDNF$ polymorphism is G-196A, which results in a change of valine to methionine at codon 66 (Val66Met). The Met allele is associated with impaired intracellular trafficking and activity-dependent secretion of $BDNF$ in neurons (Egan et al. 2003; Chen et al. 2004). A second
polymorphism, C-270T, occurs in the 5′-noncoding region of BDNF; functionality of this polymorphism is suspected, but has not been fully elucidated (Szczepankiewicz et al. 2005). Although at present the BDNF C-270T polymorphism is not known to cause changes in BDNF, the T allele is thought to affect the translation efficacy of BDNF (Kunugi et al. 2001). No data are currently available on the impact of a BDNF polymorphism distribution. The symptomatic group consisted of patients with clinical signs of WD at onset. The symptomatic group consisted of patients with clinical signs of WD at onset.

The clinical form of WD was established based on the presence and intensity of individual signs of WD at diagnosis. In symptomatic patients, a predominant symptoms scoring system at diagnosis was used as described in previous studies (Merle et al. 2007; Litwin et al. 2012). The assessment of hepatic signs and symptoms was based on a detailed questionnaire that included data on fatigue, weight loss, leg edema, jaundice, abdominal swelling, hematemesis, hemorrhaging, fulminant liver failure, and laboratory examinations (e.g., ultrasound, liver and spleen assessment, and measurement of aminotransferases, bilirubin, international normalized ratio for blood coagulation, and albumin) available from medical history and records. The evaluation of

Materials and methods

Patients and controls

We studied 414 patients diagnosed with WD at the Institute of Psychiatry and Neurology in Warsaw, Poland, between 1970 and 2010. A total of 145 healthy volunteers served as a control group. This study was approved by the local ethics committee, and informed consent was provided by all subjects included in the study. Patient diagnoses were based on clinical symptoms, abnormal copper metabolism (decreased serum ceruloplasmin and serum copper, increased 24-h urinary copper excretion), and the presence of the Kayser-Fleischer ring; many diagnoses were confirmed by genetic examination (Gromadzka et al. 2011). Clinical and family data, as well as physical, neurological, laboratory, brain magnetic resonance, and liver examination data were collected if available.

Patients with WD were divided into two groups according to the presence of clinical symptoms: presymptomatic and symptomatic. The presymptomatic group consisted of patients without clinical symptoms or signs of WD (usually siblings of the index case), and these patients were only included in the overall BDNF polymorphism distribution. The symptomatic group consisted of patients with clinical signs of WD at onset.

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Statistical analysis

Statistical analyses were carried out with STATISTICA PL (version 10.0) provided by StatSoft® (2012, Poland). Genotype and allele frequencies were compared with the chi-squared test. The Bonferroni correction for multiple comparisons was used as needed. The Mann–Whitney U test was used for comparisons of two independent groups. Results of multiple logistic regression are expressed as an adjusted odds ratio (OR) and a 95 % confidence interval (95 % CI). Significance was set at \( p \leq 0.05 \).

Results

Patient demographics and clinical characteristics

A total of 414 patients (220 women and 194 men) were enrolled in the study (Table 1). The control group consisted of 145 healthy sex- (83 females and 62 males) and age- (mean±standard deviation, 40.09±10.19 years) matched volunteers.

BDNF Val66Met and C-270T polymorphisms and WD susceptibility

No significant differences were found in the BDNF allele and genotype distributions between male and female
patients and healthy volunteers (data not shown). However, significant differences were detected in the distributions of Val66Met and C-270T alleles and genotypes between WD patients and healthy volunteers, even when Bonferroni correction for multiple comparisons was applied. None of the control subjects carried the BDNF Met/Met genotype; thus, in the patient group the Met/Met genotype was combined with the Val/Met genotype for statistical purposes (Table 2).

In logistic regression analysis, the BDNF Val/Val and −270 C/T genotypes were more frequent in patients with WD than in controls (p = 0.0001, OR 2.26, 95 % CI 1.54–3.33, and p = 0.046, OR 2.12, 95 % CI 1.01–4.45, respectively). BDNF Val/Val and −270 C/T occurred together in 10 % of WD patients and in 4 % of healthy controls (p = 0.001, OR 1.69, 95 % CI 1.53–1.86).

BDNF polymorphisms and course of WD

No differences were found in the distributions of the BDNF Val66Met and −270 C/T genotypes between patients with predominant neurological-psychiatric disease and patients with the hepatic form of the disease at diagnosis. The BDNF Val/Val genotype was detected in 68 % of WD patients with a neuropsychiatric form of the disease and in 68 % of patients with the dominant hepatic form. The BDNF −270 C/C genotype was detected in 84 % and 85 % of WD patients with the neuropsychiatric and hepatic forms of the disease, respectively. No difference was identified in the age of onset between patients with different BDNF variants, including comparisons within and between sex groups and patients with different dominant neurological symptoms of the disease (tremor-rigidity, rigidity, tremor, dystonia; Table 3).

The BDNF Val/Val genotype occurred more frequently in symptomatic patients than in presymptomatic patients. This difference became even more evident when only patients homozygous for ATP7B p.H1069Q were considered (Table 4). In this group of patients the BDNF Val/Val genotype occurred more frequently in symptomatic patients than in presymptomatic patients (logistic regression analysis p = 0.01, OR 2.71, 95 % CI 1.23–5.96).

Discussion

WD is a copper metabolism disorder that results in the formation of unstable ceruloplasmin, which is rapidly degraded. The disorder results in copper accumulation in hepatocytes (Mercer 2001). Excess copper is taken up by extrahepatic tissues, including the brain and the cornea limbus. Copper accumulation leads to the clinical manifestation of WD.

Though classically considered to be involved in the pathogenesis of neurodegenerative and psychiatric disorders, BDNF has been found outside of the central nervous system, in muscle, heart, gonads, and in systemic circulation (Matthews et al. 2009; Nakahashi et al. 2000). Increasing evidence has demonstrated a function of BDNF outside the brain, especially in metabolic health (Golden et al. 2010; Pedersen 2009). The role of peripherally circulating BDNF in WD is not known. The involvement of BDNF in oxidative processes and systemic low-grade inflammatory states may at least partly underlie BDNF’s contribution to the pathogenesis of neurodegenerative diseases with primary hepatic pathology, although this hypothesis requires verification. Elevated plasma BDNF levels in cardiovascular disease have been speculated to represent a compensatory response to underlying disease processes (Golden et al. 2010); a similar protective effect may be exerted in WD by increased BDNF levels controlled by genetic mechanisms.

To the best of our knowledge, the present study is the first to investigate BDNF polymorphisms with regard to WD susceptibility and the course of the disease. The distribution of BDNF genotypes in WD patients was similar to those described previously: 66 % for BDNF Val/Val in the current study, as compared to 65.4 % in Alzheimer’s disease (Ventriglia et al. 2002), 64 % in Huntington’s disease (Ma et al. 2006), 62.9 % in cervical dystonia (Groen et al. 2012), and 60 % in multiple sclerosis (Mirowska-Guzel et al. 2008). In the case of the BDNF C-270T polymorphism, the C/C genotype was noted in 88.2 % of Alzheimer’s disease patients (Kunugi et al. 2001) and 68 % of multiple sclerosis patients (Mirowska-Guzel et al. 2008), versus 86 % of WD patients in the current study. The distributions of these variants are considered to be stable in diseases of primary neurodegenerative pathology and in healthy volunteers. However, these previous studies were performed in ethnically diverse populations with central nervous system diseases with different underlying pathogenesis processes, at least in terms of primary or secondary neurodegeneration.

Here we have determined that the BDNF Val66Met and C-270T polymorphisms are associated with WD, acting both independently and together. The BDNF Val/Val genotype occurs more often in WD patients than in controls, but the Met allele is thought to be involved in the BDNF impairment typical of neurodegenerative diseases. It is unclear why the BDNF Val/Val genotype occurs more frequently in WD patients than in healthy controls. Although the Met allele is traditionally thought to result in decreased secretion of the peptide (Egan et al. 2003), increased secretion of BDNF in the presence of the Met allele was shown in an animal study (Lang et al. 2005). The protective role of the Met allele on working memory performance was detected in multiple sclerosis patients (Zivadinov et al. 2007) and in Parkinson’s disease patients (Fohtynie et al. 2005), and was evident in imaging-genetic studies of multiple
sclerosis patients (Cerasa et al. 2010). One explanation is that the pro-BDNF produced in the brains of Val/Val carriers potentially interferes with the mature form of BDNF, and may even inhibit BDNF maturation. Furthermore, mature BDNF promotes cell survival by activating tropomyosin-related kinase receptor B, whereas pro-BDNF preferentially binds to the p75NTR receptor and induces cell apoptosis (Beattie et al. 2002; Lee et al. 2001). As we did not measure the BDNF concentration, we are unable to examine possible correlations between either of the assessed polymorphisms and serum BDNF levels.

In the present study, no difference was found in the distribution of any of the investigated alleles and genotypes between patients with two different forms of the disease at diagnosis (hepatic or neurological). In addition, neither BDNF polymorphism was associated with any neurological symptoms typical of the disease (tremor, rigidity, dystonia) or with age of disease onset in patients with different neurological symptoms. Considering the age of disease onset, our observations were

Table 1  Wilson’s disease patient demographics and clinical characteristics

|                             | All patients (n=414) | Women (n=220) | Men (n=194) | Test statistics |
|-----------------------------|----------------------|---------------|-------------|----------------|
| Age at qualification for the study a | 40.90±12.98         | 40.60±13.30   | 41.24±12.66 | p=0.49*        |
| Age at first symptoms a     | 27.18±9.38          | 27.51±9.82    | 26.83±8.92  | p=0.93*        |
| Age at diagnosis a          | 28.45±9.86          | 28.57±10.12   | 28.31±9.58  | p=0.96*        |
| Symptomatic, n (%)          | 338 (82)            | 174 (79)      | 164 (84.5)  |                |
| Presymptomatic, n (%)       | 76 (18)             | 46 (21)       | 30 (15.5)   |                |
| Neuropsychiatric form, n (%)| 194 (57)            | 84 (48)       | 110 (65)    |                |
| Hepatic form, n (%)         | 145 (43)            | 90 (52)       | 54 (33)     |                |
| Neurological symptoms, n (%)| 224 (54)            | 105 (48)      | 119 (61)    | Chi²=7.69, df=1, p=0.0055** |
  | Discrete, n (%)             | 20 (9)              | 12 (11)      | 8 (7)        | Chi²=1.33, df=1, p=0.25** |
  | Rigidity-tremor, n (%)      | 60 (27)             | 24 (23)      | 36 (31.5)   | Chi²=1.56, df=1, p=0.21** |
  | Rigidity, n (%)             | 15 (7)              | 4 (4)        | 11 (10)     | Chi²=2.64, df=1, p=0.10** |
  | Tremor, n (%)               | 101 (46)            | 53 (50)      | 48 (42)     | Chi²=2.32, df=1, p=0.13** |
  | Dystonia, n (%)             | 28 (13)             | 12 (11)      | 16 (14)     | Chi²=0.21, df=1, p=0.65** |

*Data are presented in years as mean and standard deviation
*p value from the Mann–Whitney U test comparing women and men
**Chi-squared test comparing women and men

Table 2  Frequency of BDNF Val66Met and C-270T alleles and genotypes in Wilson’s disease patients versus healthy controls

| BDNF Val66Met  | Wilson’s disease patients n=414 (%) | Healthy controls n=145 (%) | Test statistics a |
|----------------|------------------------------------|----------------------------|-------------------|
| Allele frequency |                                    |                            |                   |
| Val            | 674 (81)                           | 211 (73)                   | Chi²=9.72, df=1, p=0.018, (p=0.036**) |
| Met            | 154 (19)                           | 79 (27)                    |                   |
| Genotype frequency |                                  |                            |                   |
| Val/Val        | 274 (66)                           | 66 (45.5)                  | Chi²=19.25, df=1, p=0.0001, (p=0.0002**) |
| Val/Met+Met/Met| 140 (34)                           | 79 (54.5)                  |                   |
| BDNF C-270T    |                                    |                            |                   |
| Allele frequency |                                  |                            |                   |
| C              | 772 (93 %)                         | 281 (97 %)                 | Chi²=5.25, df=1, p=0.022, (p=0.044**) |
| T              | 56 (7 %)                           | 9 (3 %)                    |                   |
| Genotype frequency |                                 |                            |                   |
| C/C            | 358 (86 %)                         | 136 (94 %)                 | Chi²=5.60, df=1, p=0.018, (p=0.036**) |
| C/T            | 56 (14 %)                          | 9 (6 %)                    |                   |

a Chi-squared test
b Bonferroni correction
similar to those previously made in patients with cervical dystonia (Groen et al. 2012); no associations were noted between the BDNF Val66Met polymorphism and age of onset, but a higher frequency of bilateral postural arm tremor was observed in patients with the BDNF Val/Val genotype. In contrast, we did not uncover any association between the BDNF Val66Met and C-270T polymorphisms and tremor in WD. Although BDNF is known to be widely distributed in the mammalian brain, significant differences may exist in its localization and distribution, especially in neurodegenerative disorders. In Huntington’s disease, reduced expression of BDNF occurred in the putamen and caudate compared to controls, but expression was preserved in the temporal cortex, parietal cortex, and hippocampus (Ferrer et al. 2000). No such studies have been performed with WD patients, and thus we cannot be certain whether any differences exist in BDNF expression in various brain structures in WD patients.

An interesting finding is the significant difference in the distribution of BDNF Val/Val between symptomatic and presymptomatic WD patients. The more evident difference in ATP7B p.H0169Q homozygotes can be explained by the homogeneity of our population of WD patients. The BDNF Val allele may exert a protective role, but this hypothesis requires verification by long-term observation of our group of patients.

**Table 3** Distribution of BDNF Val66Met and C-270T genotypes in Polish patients with Wilson’s disease with respect to the dominant neurological form of the disease

| Wilson’s disease patients | BDNF | BDNF | p-value | BDNF | BDNF | p-value |
|---------------------------|------|------|---------|------|------|---------|
|                           | Val/Val | Val/Met + Met/Met | C/C | C/T |
| Age at onset * | 26.65±9.51 | 26.79±9.83 | 0.77* | 26.85±9.76 | 25.83±8.67 | 0.57* |
| Age at diagnosis * | 28.53±9.51 | 28.28±10.58 | 0.68* | 28.47±10.07 | 28.30±8.56 | 0.93* |
| Dominant neurological form, n (%): | | | | | | |
| Rigidity-tremor (n=60) | 40 (67) | 20 (33) | 0.93** | 48 (80) | 12 (20) | 0.11** |
| Rigidity (n=15) | 12 (80) | 3 (20) | 0.25** | 13 (87) | 2 (13) | 0.98** |
| Tremor (n=101) | 69 (68) | 32 (32) | 0.60** | 90 (89) | 11 (11) | 0.37** |
| Dystonia (n=28) | 20 (71) | 8 (29) | 0.54** | 24 (86) | 4 (14) | 0.90** |

*Data are presented in years as mean and standard deviation

*Mann–Whitney U test for age comparisons between carriers of different BDNF Val66Met and C-270T genotypes

**Chi-squared test for distribution of WD forms between different BDNF Val66Met and C-270T genotypes

**Table 4** Distribution of BDNF Val66Met and C-270T genotypes in symptomatic and presymptomatic Wilson’s disease patients harboring the ATP7B 1069 HQ/HQ genotype

| BDNF Val66Met | | |
|---------------|--|--|
| Allele frequency | | |
| Val | 262 (86) | 51 (75) |
| Met | 44 (14) | 17 (25) |
| Genotype frequency | | |
| Val/Val | 115 (75) | 18 (53) |
| Val/Met+Met/Met | 38 (26) | 16 (47) |
| BDNF C-270T | | |
| Allele frequency | | |
| C | 284 (93) | 64 (94) |
| T | 22 (7) | 4 (6) |
| Genotype frequency | | |
| C/C | 131 (86) | 30 (88) |
| C/T | 22 (14) | 4 (12) |

*Chi-squared test

**Yates correction for fewer than five samples
In conclusion, the results of the present study suggest that genetically determined BDNF functions may be related to the occurrence of WD but not with its course or symptomatology. However, large variations in the age of onset and clinical manifestation of WD make this hypothesis difficult to investigate. The other major limitation of the current study is due to this study’s ability to detect only the association of two particular BDNF polymorphisms with WD, similar to many other studies; however, these relationships are difficult to explain on a molecular level. We cannot exclude the possibility that the observed effect is due to another gene located near BDNF on the chromosome, as pathogenic mutations in a neighboring gene causing or modifying WD could be overlooked by this study design. To validate the present results, further studies are needed to elucidate the role and mechanism of BDNF action in WD susceptibility and disease course.

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Conflict of interest The authors declare no conflicts of interest.

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