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The effect of gender on brain MRI pathology in Wilson's disease

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Abstract Gender influence on the clinical manifestations of Wilson's Disease (WD) has been suggested; however, brain MRI pathology based on sexual dimorphism in WD has not yet been examined. The aim of this study was to analyse the effect of gender on brain MRI pathology according to the predominant form of WD. We retrospectively analysed the brain MR images of 204 newly diagnosed and untreated WD patients. The predominant form of the disease was neuropsychiatric (n=105), hepatic (n=67) or presymptomatic (n=32). Overall, neuroimaging pathologies were found in 64.2 % WD patients. The clinical form analysis revealed significant gender-related differences. In the neuropsychiatric form, men presented with cerebellar atrophy and cortical brain atrophy more often than women (25/58 vs. 11/47; p<0.05) and (23/58 vs. 12/47; p=0.09), respectively. In contrast, women tended to present with globus pallidus lesions more often than men (25/47 vs. 20/58; p=0.054). There were no gender differences observed in the hepatic form, but cortical brain atrophy presented more often in men than women (3/12 vs. 0/20; p<0.05) in the presymptomatic form. According to our findings, there is a gender-dependent brain vulnerability to copper toxicity. We speculate that these differences are potentially related to an oestrogen protective effect and are due to differences in gender-related clinical forms.

Keywords Wilson's disease · Magnetic resonance imaging · Neuroimaging · Gender differences

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Introduction

Wilson disease (WD) (OMIM 277900), which is also known as hepatolenticular degeneration, is an autosomal recessive disorder with copper metabolism disturbances that result in copper accumulation in many tissues (brain, liver, cornea) and secondary damage to affected organs (Pfeiffer 2007). In the brain, pathological changes are mainly localised in the basal ganglia; however, copper accumulates in all brain regions. In WD patients with neurological signs (Machado et al. 2006), localisation of brain magnetic resonance imaging (MRI) lesions are well described (King et al. 1996; Da Costa et al. 2009; Prashanth et al 2005; Magalhaes et al. 1994; Saatci et al. 1997; Prayer et al. 1990; Marsden 1987) but the clinical significance of these findings remains unclear. Published MRI studies of WD have shown a number of abnormalities, including focal atrophy, high intensity lesions and hypointense areas on T2-weighted imaging (King et al. 1996; Da Costa et al. 2009; Prashanth et al 2005; Magalhaes et al. 1994; Saatci et al. 1997; Prayer et al. 1990). Typical WD brain MRI changes are described as symmetrical T2 hyperintensity or mixed intensity in the putamina (with a hyperintense peripheral putamina rim) and globi pallidi, caudate nuclei, thalami and pons. The midbrain, cerebellum, corticospinal tracts, cortex and subcortical areas were also affected. In addition, the T1 signal was generally reduced in the basal ganglia (King et al.

1996). Unfortunately, these observations are only based on a small group of patients with neurological symptoms. Moreover, there are only a few studies that have attempted to characterise MRI abnormalities in WD and correlate their findings with symptoms and localisations of the lesions, and these conclusions are often conflicting (King et al. 1996; Magalhaes et al. 1994; Saatci et al. 1997; Walshe 1986)

Gender MRI brain differences have been previously reported in healthy people. Men have a greater brain (mainly white matter, the amygdala, hypothalamus and frontomedial cortex) and cerebrospinal fluid volume, with a greater age-related loss in brain volume (specifically in the frontal and temporal lobes) (Cerghet et al. 2009; Goldstein et al. 2001; Schlaepfer et al. 1995; Zaidi 2010; Franklin et al. 2000). In contrast, women have higher proportions of grey matter compared to the whole brain volume, larger volumes of regions associated with language (dorsolateral prefrontal cortex; superior temporal gyrus) and a larger splenium of the corpus callosum. In addition to anatomical differences, there are also data indicating differences in gender-related brain and glucose metabolism, as observed in regional blood flow in positron emission tomography (PET) and some advanced MRI techniques (Cerghet et al. 2009; Goldstein et al. 2001; Schlaepfer et al. 1995; Zaidi 2010; Franklin et al. 2000). These differences are also explained by the action of sex hormones on brain development and metabolism. Both testosterone and oestrogen are involved in brain development and act through different receptors (the androgen and oestrogen receptors, respectively), which are located in different brain regions, to produce structural differences (Cerghet et al. 2009; Goldstein et al. 2001; Schlaepfer et al. 1995; Zaidi 2010; Franklin et al. 2000).

Recently, growing evidence has suggested the existence of gender differences in the clinical course of neurodegenerative and neuroinflammatory disorders. It is hypothesised that these differences are mainly related to oestrogens (Shulman 2007) and different brain iron metabolism (Xiaojun et al. 2008; Kovalev et al. 2003; Litwin et al. 2012a). Among neurological disorders, such differences are very well documented in Parkinson's disease (PD), Lewy Body Disease (LBD), Alzheimer's disease (AD), multiple sclerosis (MS) and Wilson's disease (Shulman 2007; Xiaojun et al. 2008; Kovalev et al. 2003; Litwin et al. 2012a, b; Hafner 2003; Nasrallah et al. 1990; Tomassini et al. 2005).

In neuropsychiatric disorders, there are some conflicting data regarding gender differences in brain MRI. For example, in schizophrenia, males more often present with brain atrophy and enlarged ventricles (although some studies claim that these symptoms are predominant in women) (Hafner 2003; Nasrallah et al. 1990). All of these radiological findings may be due to different gender-related courses of the disease, which is very well documented in the literature (Hafner 2003; Nasrallah et al. 1990). Furthermore, in multiple sclerosis (MS), there are data suggesting that sex hormones modulate brain damage during the disease course. In MS, MRI studies have suggested associations between testosterone levels and the number of gadolinium-enhanced lesions in women and between estradiol levels and brain damage in men (Tomassini et al. 2005). Currently, there is lack of studies investigating MR gender differences in other neurological disorders, although clinical gender differences support the idea that sex-hormones may modulate brain damage and be an important factor that affects disease presentation.

Because sexual dimorphism in brains is observed in the course of many disorders (e.g., schizophrenia and MS), we performed a study aimed to analyse gender differences in untreated WD patients using brain MRI.

Patients and methods

In this retrospective study, 204 consecutively newly diagnosed WD patients were recruited between 1988 and 2010. Patients involved in this study were not treated with anti-copper drugs until MRI examination. The patients were diagnosed with WD based earlier on clinical symptoms, abnormal copper metabolism (decreased level of serum caeruloplasmin and serum copper, increased 24 h urine copper excretion), the presence of the Kayser-Fleicher (K-F) ring and, in many cases, a genetic examination. In doubtful cases, the diagnosis was confirmed by measuring the incorporation of Cu64 into caeruloplasmin at 24 and 48 h. All the WD diagnoses were also reviewed and confirmed with Ferenci score (Ferenci et al. 2003). All of the laboratory measurements of copper metabolism were performed in the same laboratory using similar methods (colourimetric enzymatic assay of caeruloplasmin in serum, Ravin's method; atomic adsorption spectroscopy for copper levels in serum and urine) as described previously (Gromadzka et al. 2005, 2006).

A routine brain MRI was performed in all cases at the time of WD diagnosis. Conventional MR imagers with standard head coils and routine brain protocols were performed. The MR images obtained were collected in our institution and analysed retrospectively by 2 neuroradiologists, who were blinded to the patients' clinical information. Abnormalities in the brain parenchyma were divided into six groups: putamen, globus pallidus, caudate nuclei, cerebellum, thalamus and pons. The WD lesions were assessed as hypointensive and hyperintensive (or rarely, hypointensive) in T1- and T2-weighted sequences, respectively. The presence of atrophic changes (dilatation of the lateral ventricles, widening of the sulci and cisterns) were divided as follows: cortical brain atrophy, cerebellar atrophy and

widening of the ventricles were visually assessed subjectively in the T1-weighted sequences. The presence or absence of brain pathology were scored as: "0"—no abnormality and "1"—changes in signal intensity or presence of atrophic changes.

For specific neuroimaging results, analytical differences in patients were divided into the following groups:

1) according to clinical form at diagnosis—hepatic, neuropsychiatric, or presymptomatic
2) according to gender—men or women

The symptomatic group contained patients with clinical signs of WD at diagnosis, and the presymptomatic group consisted of patients without clinical pathology, suggesting WD at diagnosis (usually with a family screening). The predominance symptoms scoring system at diagnosis was the same like in previous WD papers (Litwin et al. 2012a). The hepatic symptoms and signs assessment was based on detailed questionnaire which included data on: fatigue, weight loss, legs oedema, jaundice, abdominal swelling, haematemesis, haemorrhages, fulminant liver failure, as well as laboratory examinations (ultrasound examinations—liver and spleen assessment, aminotransferases, bilirubin, INR, albumen), that were available from medical history and records. Neuropsychiatric symptoms and signs evaluation was also based on detailed questionnaire which included data on signs like: salivation, dysphagia, speech, writing and gait disturbances, adynamia, epileptic seizures, involuntary movements, mood disorders, anxiety and cognitive impairment Neurological symptoms were assessed and ranged from: 0—completely normal to 3—severely impaired. Hepatic symptoms were assessed and ranged in four categories: 0—completely normal; 1—increased level of liver enzymes without signs of liver cirrhosis; 2—compensated liver cirrhosis, 3—decompensated liver cirrhosis or acute liver failure. Patients with hepatic or neurological score of >1 were classified according higher score, in case the equal result patient were classified as neurological case.

All of the classifications were determined by the same group of neurologists in our department.

Statistical analysis

All of the data were analysed using Statistica v.9.0 statistical software (StatSoft, Cracov, Poland). The mean, range, percentage, and standard deviation (SD) were noted in the descriptive summary statistics. Quantitative variables were compared using the Mann-Whitney *U*-test. Categorical variables were compared between groups using the chi-square test and Fisher's test; $p<0.05$ was considered significant and $p<0.1$ was borderline significant. For multiple comparisons, hypothesis testing was performed using the Bonferroni correction (the *p*-value divided by the total number of pairwise comparisons) to correct for the possibility that in multiple comparisons, the null hypothesis would be rejected by chance.

Results

The demographic data, baseline gender differences and clinical characteristics of 204 patients included in this study are given in Table 1.

Clinical forms of WD and MRI results

Overall, neuroimaging pathology was found in 131 patients (64.2 %). There were 105 patients with the neuropsychiatric form of WD and MRI abnormalities were found in 95 patients (90.4 % cases). There were 67 patients in the hepatic group, and brain pathology was found in 28 patients (41.7 % cases). There were 32 WD patients with the presymptomatic form, and brain pathology was found in only 8 patients (25 %). Further details on data pertaining to the clinical forms and brain pathology are presented in Table 1.

The localisation and forms of MRI findings were also determined in 131 cases. We found lesions in the putamen in 66 (50 %) cases, globus pallidus in 59 (45 %) cases, pons in 55 (41.9 %) cases, and thalamus in 53 (40 %) cases. Atrophy was observed in the cerebellum in 47 (35.8 %) cases and in the cortical brain in 42 (32 %) cases. Ventricular widening appeared in 39 (29.7 %) cases, and lesions in the caudate nuclei and cerebellum were observed in 30 (22.9 %) and 11 (8.3 %) cases, respectively (Table 2).

Gender and MRI results

The localisation of MRI brain lesions and atrophy in male and female WD patients with neuropsychiatric, hepatic and presymptomatic forms is presented in Tables 2, 3 and 4.

Analysis of patients with the neuropsychiatric form indicates a predominance of cerebellar atrophy ($p<0.05$) and a tendency toward cortical brain atrophy ($p=0.093$) in men; however, lesions in the globus pallidus lesions predominantly occur in women ($p=0.054$) (Table 2).

We did not find any gender differences in brain MRI abnormalities in the hepatic form of the disease (Table 3), however, presymptomatic patients exhibited a predominance of cortical brain atrophy in men ($p<0.05$). After performing the Bonferroni correction for multiple comparisons, none of the observed differences were significant.

Table 1 Clinical data, baseline gender differences and demographic characteristics of WD patients included in the study (n=204)

Clinical form	Male/female ratio	Age of onset[a]	Age of diagnosis[a]	Disease latency[b]	Pathological MRI findings (%)
Hepatic (n=67)	31/36	All 24.7 (8–55) Male 23.4 (8–44)	All 28.5 (6–60) Male 28.6 (17–44)	All 3.9 (0–5) Male 4.7 (0–27)	41.7 % (28/67)
		Female 25.8 (14–55)	Female 28.5 (6–60)	Female 3.3 (0–20)	
Neuropsychiatric (n=105)	58/47	All 30.8 (14–57) Male 30.9 (15–55)	All 33.5 (17–63) Male 33.7 (17–56)	All 2.7 (0–15) Male 2.8 (0–15)	90.4 % (95/105)
		Female 30.7 (14–57)	Female 33.4 (21–63)	Female 2.6 (0–10)	
Presymptomatic (n=32)	12/20	N/A	All 23.8 (13–43) Male 20.1 (8–34)	N/A	25 % (8/32)
			Female 24.0 (13–43)		
All patients (n=204)	101/103	All 28.0 (8–57) Male 28.2 (13–57)	All 30.4 (6–63) Male 29.9 (6–63)	Male 2.8 (0–20)	64.2 % (131/204)
		Female 27.9 (8–55)	Female 30.9 (16–56)	Female 3.4 (0–27)	

[a] Values are means with ranges in parentheses

[b] The disease latency—the time between first symptoms onset and disease diagnosis

Discussion

Based on data obtained from 204 patients, this is one of the largest neuroimaging studies of WD patients conducted. We confirmed a high ratio of MRI brain findings in WD patients—generally in 64.2 % of cases. As expected, there were differences according to the clinical form of the disease. Abnormalities in the neuropsychiatric, hepatic, and presymptomatic forms were identified in 90.4 %, 41.7 % and 25 % of the cases, respectively.

In general, we found less frequent brain MRI abnormalities compared with previous reports (King et al. 1996; Da Costa et al. 2009; Prashanth et al 2005; Magalhaes et al. 1994; Saatci et al. 1997; Prayer et al. 1990; Kozic et al. 2003), which may be due to differences in the methods of patient selection, the examination performed at diagnosis, patients with all of the clinical manifestations (hepatic neuropsychiatric and presymptomatic), and the large number of cases. Until now, most studies have presented data obtained mainly from neurological patients (Machado et al. 2006; King et al. 1996; Da Costa et al. 2009; Prashanth et al 2005; Magalhaes et al. 1994; Saatci et al. 1997), with very few patients exhibiting the hepatic form of the disease (Kozic et al. 2003). We believe that our data are not deeply biased by our hospital speciality because we had approximately 30 % of patients with hepatic manifestation at diagnosis. In our centre, we diagnosed WD regardless of the clinical manifestations. However, previous studies have shown different positive and negative data, providing correlations between the localisations of brain lesions in WD and clinical symptoms (Kozic et al. 2003; Sinha et al. 2007; Hitoshi et al. 1991; Alanen et al. 1999; Sudmeyer et al. 2006). However, there has been a lack of data regarding gender differences in WD. We found several gender differences in the brain MRI examinations, which are specifically related to the predominant clinical forms of the disease. Neuropsychiatric men presented neurodegenerative signs more often than women, including cortical brain atrophy and cerebellar atrophy. We did not observe these correlations in the hepatic form; however, cortical brain atrophy

Table 2 The gender differences between the localization of MRI findings in neuropsychiatric WD patients

Localization	Men (n=58)	Women (n=47)	p-value
Putamen (lesions)	26 (44 %)	27 (57 %)	0.198
Globus pallidus, (lesions)	20 (34 %)	25 (53 %)	0.054
Caudate nucleus (lesions)	11(18.9 %)	12 (25 %)	0.418
Cerebellum (lesions)	6 (10 %)	4 (8.5 %)	0.750
Thalamus (lesions)	26 (44.8 %)	24 (51 %)	0.524
Cerebellum (atrophy)	25 (43 %)	11 (23 %)	0.034
Ventricular widening	23 (39 %)	13 (27 %)	0.197
Pons (lesions)	25 (43 %)	23 (48.9 %)	0.550
Brain cortex (atrophy)	23 (39 %)	12 (25 %)	0.093

p for significance after Bonferroni correction: 0.002

Table 3 Gender differences between the localization of MRI findings in hepatic WD patients

Localization	Men (n=31)	Women (n=36)	p-value
Putamen (lesions)	7 (22 %)	3 (8 %)	0.168
Globus pallidus (lesions)	5 (16 %)	4 (11 %)	0.722
Caudate nucleus (lesions)	3 (9.6 %)	3 (8 %)	1.000
Cerebellum (lesions)	1 (3 %)	0 (0 %)	0.462
Thalamus (lesions)	0 (0 %)	2 (5 %)	0.495
Cerebellum (atrophy)	2 (6 %)	6 (16 %)	0.270
Ventricular widening	0 (0 %)	2 (5 %)	0.495
Pons (lesions)	2 (6 %)	2 (5 %)	1.000
Brain cortex (atrophy)	1 (3 %)	3 (8 %)	0.617

p for significance after Bonferroni correction: 0.002

occurred more often in presymptomatic men. Such observations could be very important in determining the course and prognosis of WD neuropsychiatric signs because brain atrophy is now used as a biomarker of disease progression in many neurological disorders, such as multiple sclerosis, PD and Alzheimer disease (Tomassini et al. 2005; Dalaker et al. 2009; Miller and Cronin-Golomb 2010). In previous WD studies, brain MRI atrophic changes have been reported from 82 % (King et al. 1996) to 25 % in the hepatic form (Kozic et al. 2003). The occurrence of MRI atrophic changes has been proposed to be related to the clinical predominant form, particularly when the disease was untreated and neuropsychiatric symptoms appeared (Da Costa et al. 2009). The more frequent occurrence of brain cortical atrophy and cerebellar atrophy in WD men compared to women may be explained by gender-related differences in clinical presentation. There is a higher frequency of neuropsychiatric signs observed in men and of hepatic signs in women (Litwin et al. 2012a, b). According to previous data regarding brain atrophic changes and neuropsychiatric signs, these observations may explain why men present neurodegenerative signs in the brain more often than women (Hafner 2003; Nasrallah et al. 1990). Such mechanisms may also underlie gender differences in the presymptomatic group because some of the presymptomatic patients initially exhibited WD symptoms, and there is a greater possibility for men to initially display neuropsychiatric symptoms. Second, atrophic changes in the presymptomatic group could identify WD men who are vulnerable to symptoms (for example, because of a lack of compliance). Further studies regarding the changes in presymptomatic patients related to gender are needed to verify these hypotheses.

Atrophic gender-related neuroimaging pathology has been previously reported to significantly occur in other neuropsychiatric disorders such as schizophrenia (Hafner 2003; Nasrallah et al. 1990) and may be explained by both oestrogen neuroprotective effects and differences in brain iron metabolism. In the brain, oestrogens act in the following ways: 1) as neurotrophins for dopaminergic neurons; 2) as antioxidants to protect cells against toxic metabolites; and 3) in dopamine synthesis, affecting uptake and dopamine receptor expression (decrease of D2 receptors and increase of the dopamine transporter density) (Miller and Cronin-Golomb 2010). The "oestrogen protective hypothesis" is strongly supported by clinical and experimental observations in extrapyramidal disorders. Extrapyramidal disorders are a less frequent occurrence of Parkinson's disease that is typically displayed at a later onset (2 years) in women and exhibit differences in their major clinical signs (Shulman 2007; Miller and Cronin-Golomb 2010). Iron brain metabolism gender-related differences have also been proposed in the aetiology of many neurodegenerative disorders (Xiaojun

Table 4 Gender differences between the localization of MRI findings in presymptomatic WD patients

Localization	Men (n=12)	Women (n=20)	p-value
Putamen (lesions)	2 (16 %)	1 (5 %)	0.540
Globus pallidus (lesions)	3 (25 %)	2 (10 %)	0.708
Caudate nucleus (lesions)	0 (0 %)	1 (5 %)	1.000
Cerebellum (lesions)	0 (0 %)	0 (0 %)	–
Thalamus (lesions)	0 (0 %)	1 (5 %)	1.000
Cerebellum (atrophy)	2 (16 %)	1 (5 %)	0.375
Ventricular widening	1 (8 %)	0 (0 %)	0.094
Pons (lesions)	1 (8 %)	2 (10 %)	1.000
Brain cortex (atrophy)	3 (25 %)	0 (0 %)	0.044

p for significance after Bonferroni correction: 0.002

et al. 2008; Bartzokis et al. 2007; Bruehleimer et al. 2000). Ferritin iron brain metabolism is different in men and women (Xiaojun et al. 2008). This problem is not well known in WD patients, but iron gender differences are thought to contribute to WD symptoms. It is well known that the human iron brain level increases with age and in many neurodegenerative disorders, specifically in the subcortical and cortical grey matter (Xiaojun et al. 2008; Bartzokis et al. 2007; Bruehleimer et al. 2000). In addition, there are differences between healthy men and women in brain ferritin iron accumulation (Xiaojun et al. 2008; Bartzokis et al. 2007). Bartzokis showed that women have a lower brain iron ferritin level compared to men (Bartzokis et al. 2007) and attributed this difference to a menstruation protective mechanism. Brain ferritin iron has been proposed to be a risk factor for neurodegenerative disorders in men. In a PET study, Bruehleimer et al. showed that WD patients have increased brain iron uptake (Bruehleimer et al. 2000) due to a deficiency of WD copper-dependent enzymes in the mitochondria, which results in compensation by upregulation of iron-dependent enzymes. The side effects of this mechanism include a higher level of iron in the tissues of the brain and liver (Litwin et al. 2012c; Bartzokis et al. 2007). According to the findings of Bruehleimer and Bartzokis (Bruehleimer et al. 2000; Bartzokis et al. 2007), WD caused increased brain iron uptake, which resulted in the increased risk of neurodegeneration, specifically in men (who lack iron protective mechanisms). Thus, our MRI brain observations in WD patients partially confirmed these observations; the greater prevalence of neurodegenerative signs in men indicates gender differences in the brain susceptibility of this disease.

This hypothesis is also strongly supported by clinical WD observations; men present with the neuropsychiatric predominant form more often than women. Conversely, women present hepatic signs more often than men (Litwin et al. 2012a, b). The second unexpected observation in the brain MRI analysis was that lesions of the globus pallidus tended to occur more often in neuropsychiatric women than men. This observation may be explained by liver injury, which can produce hyperintense globus pallidus changes, producing secondary symptoms and neuropsychiatric signs. Furthermore, women more often present hepatic signs; correspondingly, they also present globus pallidus changes more often.

In this study, there are a few limitations. First, there is a limited number of patients, which may have produced statistically insignificant results after the Bonferroni correction. Second, there was a lack of quantitative MRI analysis and a very long period of retrospective observation (different MRI devices). However, WD is a rare disease, and the number of patients included in our analysis is greater than those in the MRI studies (Kozic et al. 2003). The study was based on a retrospective analysis, so there was no possibility to perform a prospective quantitative analysis of the atrophic changes. In the present report, we present the initial results and hypothesise about gender effects on brain MRI pathology in WD; however, this issue should be further investigated in prospective MRI studies that include new MR techniques.

Conclusions

Taken together, WD patients with MR abnormalities in their brains consist of mainly patients with the neuropsychiatric form of the disease; however, some patients also presented with the hepatic and presymptomatic forms. Changes were mainly localised to the basal ganglia, pons and thalamus, but brain cortical and cerebellar atrophy were also present. Some brain MRI gender differences were observed. Men predominantly demonstrated the neuropsychiatric form with cerebellar and cortical brain atrophy more frequently compared to females who more often exhibited lesions of the globus pallidus. There were no gender-related differences in the hepatic predominant form, but presymptomatic patients displayed cortical brain atrophy more often in men. We propose that gender differences based on the brain MRI results of WD patients are due to gender-related differences in the clinical manifestation of the disease as a result of the protective effects of oestrogens and iron metabolism differences.

Conflict of interest The authors declare not potential conflict of interests relevant to this article.

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