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Sex and Gender Differences in Parkinson's Disease and the Conclusions we should Draw

Marita F. Thiel* and Wolfgang H. Jost

Parkinson Klinik, Ortenau, Germany

Abstract

Studies in recent years suggest that in Parkinson's disease there is a distinction between the sexes. As a preliminary step we examined the data of 100 male and 100 female Parkinson's patients from a dedicated Parkinson's hospital. On the one hand, we found significant differences in their levodopa dose equivalent: This was distinctly lower for the female patients, whereas depression occurred more frequently in the female group. On the other hand, data on serum values for vitamin B12 and vitamin D as well as on the results of the test for orthostatic dysregulation and a sonographic examination of residual urine failed to show any significant differences. Our literature search revealed differences in the extent of motor and non-motor symptoms as well as in subjectively reported quality of life. These results however do have some discrepancies that will have to be clarified in future studies. For years now, the lower incidences in the female patients have suggested the possible relevance of estrogen. Precisely because women are less frequently afflicted, a possible neuroprotective role of estrogen has been discussed. In this respect the duration of estrogenic exposition, that is, the earlier or later occurrence of menopause, might be playing a role here. More recent work has also highlighted the function of the RORA receptor (retinoic acid receptor-related orphan receptor alpha). A neuroprotective function has been attributed to this receptor which is found in the pars compacta of the substantia nigra. Because its expression is subject to control from sex hormones, it might play a role in neurodegenerative diseases. Genetic studies also offer highly promising aspects: Parkinson's disease in women is more often associated with an altered variant of the gene coding for glucocerebrosidase (GBA) as well as the LRRK2 gene (leucine-rich repeat kinase 2). Further subgroups may also be significant here. The current study data thus reveals different perspectives on Parkinson's disease in men and women. Final clarification needs further work in the future.

Keywords: Gender differences • Parkinson's disease • Alzheimer's • Neurodegeneration

Introduction

Parkinson's disease is worldwide the second most frequent neurodegenerative disease, second only to Alzheimer's disease. It has been estimated that as of the year 2030 more than nine million persons will have contracted the disease [1]. We can readily assume that this will involve an ever-increasing burden for health economics, especially if calls for individualized therapies expand. The cardinal symptoms of the disease consist of rigor, tremor and akinesia, all of which can be accompanied, at any of the stages of the disease, by non-motor symptoms, that is, autonomic and/or neuropsychiatric symptoms. In the advanced stages, late motor complications such as fluctuations in the efficacy of medication and dyskinesias occur frequently. The individual patients' symptoms, the course of their disease and their response to medication are characterized by a high degree of heterogeneity. We aim at developing individually tailored treatment therapies which necessitate recognizing the possible variations of the disease well ahead of any individualized treatment. For a considerable length of time there has been a lively discussion of such topics as sex-specific as well as gender-specific differences in the incidence, the symptomatology, the response to medication and the course of idiopathic Parkinson's syndrome. Could this discussion signalize the beginning of individualized treatments in the future? Or: Are we really just not advanced enough to understand the basic underlying pathophysiology of Parkinson's disease and thus cannot yet adequately fathom gender-specific differences?

Methods

***Address for Correspondence:** Marita F. Thiel, Parkinson Klinik, Ortenau, Germany, Email: m.thiel@parkinson-klinik.de*

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Do we need a sex and gender-associated focus for treating Parkinson's disease?

Cardiology has been demonstrating for years now that infarction in females can be reliably distinguished from those in men as regards symptoms, pathophysiological mechanisms and the outcome. As a result attention has grown for female infarction, thus improving its diagnosis, and the incidence rate in women increased correspondingly [2]. We now have preliminary indications, and the real hope, that similar progress is slowly developing for neurodegenerative diseases and particularly for Parkinson's disease. In addition to the idea of gender-specific differences, another concept has taken on similar relevance: That of socio-cultural imprinting, in the sense of a fundamental gender definition. But within the framework of medical studies, the full influence of the gender aspect is quite complex and thus difficult to fully appreciate. As a result it is often neglected. Because we are only just starting to research the question of sex and gender-specific differences in idiopathic Parkinson's disease, and because so many intriguing questions remain, one ideal starting point entails the analysis of defined and replicable data and criteria. The American National Institute of Health (NIH) emphasized in May 2014 that in preclinical research Sex as a Biological Variable (SABV) must be given consideration [3]. From the viewpoint of a feministic, gender-oriented medicine, the simple binary distinction between the two sexes fully neglects the impact of social sexual norms, sex-based behavior and powerful gender-associated influences on biology and health [4], but, in our view, being aware of this distinction opens the door at the same time for a medical science in which women are not just forgotten by being automatically integrated into the category of "70 kilogram heavy, standard male patient". Precisely because men diagnosed with Parkinson's are overrepresented in the population, their involvement in studies is consistently higher and women are thus underrepresented which means that most study data describe male pathophysiology. Furthermore, studies which do permit for equal male and female participation routinely summarize their results as a single overall average. A separate treatment of the male versus the female data is more the exception rather than the standard procedure.

As a case in point: For centuries children were simply treated as small versions of adults until the physician Paul Grosser did ground-breaking post-doctoral research in 1919 at the University of Frankfurt on the topic

of pediatrics. More than 120 years later the field of pediatrics has become a large-scale and accepted field of study in its own right. Women and men, on the other hand, are still subsumed into a "one size fits all" type of approach in research. One task for our future work will be to ask whether that approach is really appropriate. Similarly, treating transgender persons deserves proper attention: They possibly need a special level of sensitivity on our part, in particular when metabolic processes have been altered exogenously.

In the pharmacological treatment of Parkinson's disease it has become more and more standard procedure to calculate dosages according to the patients' sex and weight. For women this entails 5 mg of levodopa per kilogram of bodyweight, and for men preferably 7 mg of levodopa per kilogram. This allows for an approximate evaluation for the maximum dose. In their study from 2005 Zappia and coworkers were able to demonstrate that female patients tend more towards peak-dose dyskinesias than male patients do. The authors identified female sex and higher levodopa dosages as a risk factor [5]. But there are to date yet no studies as to whether women, whose levodopa dose has in fact been selected on the basis of their weight and their sex, do have less tendency to peak-dose dyskinesias. In addition to levodopa we have a number of other pharmacological treatment strategies for Parkinson's syndrome, including the groups of MAO-B and COMT inhibitors as well as the class of dopamine agonists. A further important medication is seen in amantadine. But at the present status of research we cannot judge at all whether the dosage of these agents should be decided in dependence on sex and weight considerations. This question is further complicated by the fact that some of these drugs are only available on the market in a single dosage, thus precluding any readjustment of the dosage.

Results

Data from our clinic

We analysed data from 200 patients, 100 males and 100 females, relying on standard data routinely surveyed for all in-patient treatments at our hospital: Age, stage of the disease according to Hoehn and Yahr and the duration of the disease. In addition we compared data from all examinations then regularly performed during the patients' stay. This analysis showed an average begin of the disease for men to be at 70 years (70.42 years), while the women rather became ill at the age of 73 (72.64). As to the distribution among the different types (akinesia-rigor (AR), equivalence (ART) and tremor dominance types (T) we found no significant differences between the sexes (Figure 1).

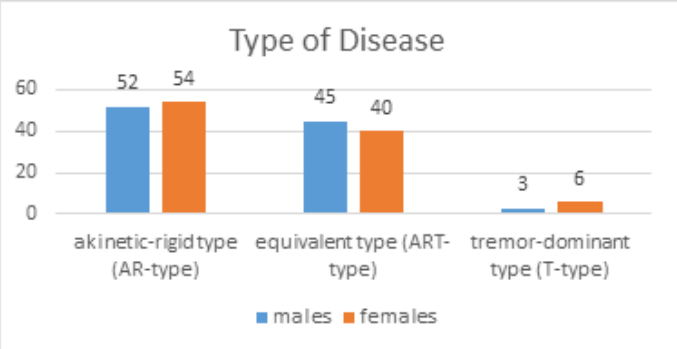

Figure 1. Type of disease

The distribution according to Hoehn and Yahr failed to show any significant differences according to sex. A bias in favor of Stages III and IV is typical for our clinic: Patients in these stages on the one hand strongly require pharmacological adjustments and activating interventions (such as physical, occupational and speech therapies) and on the other they are also sufficiently stable for a hospitalization which highlights such training (Figure 2).

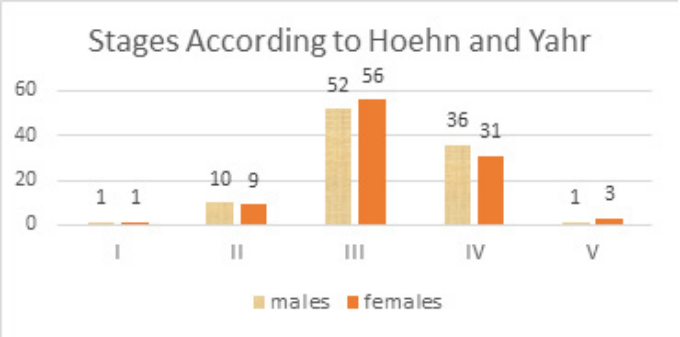

Figure 2. Stages According to Hoehn and Yahr

A significant difference was found for the Levodopa Equivalent Dose (LED) between men and women at the time of their dismissal. Compared to the LED at the time of admission, the pharmacological dopaminergic dosage at dismissal is meant to substantially improve the motor and non-motor symptoms. For the purpose of comparing the different doses we make use of the conversion table from Nyholm and coworkers (Tables 1and 2) [6].

Table 1. Statistical analysis: Equivalent dose

The Equivalent Dose				
		t-Test for mean equality		
		Significance		Average
		One-tailed p	Two-tailed p	Difference
	Variances are identical	<0.001	<0.001	204,210
Equivalent Dose	Variances not identical	<0.001	<0.001	204,21

A further difference appeared for the frequency of depression: Our analyses revealed a significantly higher occurrence in female patients at a small effect. This corresponds to the tendency seen in currently available studies (see Table 8: Motor and Non-motor symptoms) (Figure 3) (Tables 3 and 4).

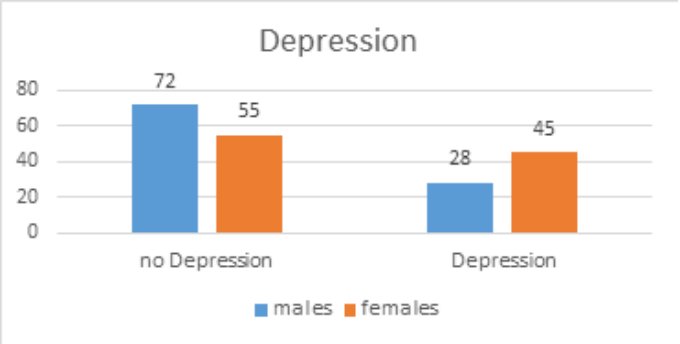

Figure 3. Depression in men and women diagnosed with Parkinson's

Female patients had significantly lower equivalent doses (average effect) compared to male patients. Various reasons can be given for this: Possibly, the sex and weight-adapted levodopa dose (which in clinical everyday life is the standard strategy for appropriate treatment) might be playing a role here. Or: Differences in the degree of disease severity, the extent of symptoms, or even potential differences in metabolism of the dopaminergic medication in men and women may be implicated here. On this point we find it interesting to compare the serum levels for vitamin B12 (Tables 5 and 6).

Here there were no significant differences between the sexes. Likewise there were no significant results for either the sonographic determination of residual urine or the results of the testing for orthostatic hypotension (Table 7).

Table 2. Statistical analysis: Equivalence dose

Effect Sizes for Independent Samples					
		Standarda	Evaluation	95% Confidence Interval	
					<0.001
Equivalent Dose	Cohen's d	338,852	0.603	0.318	0.885
	Hedges' Correction	340,142	0.600	0.317	0.882
	Glass' Delta	293,910	0.695	0.400	0.987
Note: The effect size used for the evaluation. For 'Cohen d' the cumulated standard deviation is used. For Hedges Correction the cumulated standard deviation is used with a correcting factor. For the Glass-Delta the standard deviation of the sample of the control group (the second group) is used.					

Table 3. Depression in men and women diagnosed with Parkinson's

	Value	df	Asymptomatic	Glass' Delta	Glass' Delta
Significance	Glass' Delta	Glass' Delta	Glass' Delta	Glass' Delta	Glass' Delta
(two-tailed)	Exact	Glass' Delta	Glass' Delta	Glass' Delta	Glass' Delta
Significance (two-tailed)	Exact	Glass' Delta	Glass' Delta	Glass' Delta	Glass' Delta
Significance (one-tailed)	Glass' Delta	Glass' Delta	Glass' Delta	Glass' Delta	Glass' Delta
Pearson-Chi Square	6.234a	1	0.013		
Continuity Correction	5.523	1	0.019		
Likelihood Quotient	6.278	1	0.012		
Exact Test after Fisher				0.018	0.009
Coherence linear-with-linear	6.203	1	0.013		
Note: 0 Cells (.0%) have an expected frequency of less than 5. The minimum expected frequency is 36.50. b. Is calculated only for a 2 × 2 table					

Table 4. Statistical analysis: Symmetric Measurements

Symmetric Measurements			
		Value	Approximate significance
Nominal-bzgl. Nominalma ß	Phi	-0.177	0.013
	Cramer-V	0.177	0.013
Number of valid cases		200	

Table 5. Levels of vitamin B12

Vitamin B12				
Number		Sex		total
		female	males	
Vit B12	Norm	94	90	184
	Deficient	4	9	13
	Raised	2	1	3
Total		100	100	200

Table 6. Levels of vitamin D

Vitamin D				
Number		Sex		total
		female	male	
Vit D	Norm	75	78	153
	Deficient	25	21	46
	Raised	0	1	1
Total		100	100	200

Table 7. Orthostatic hypotension

Test for orthostatic hypotension				
		Sex		total
		female	male	
Results	Norm	46	40	86
	orthostatic	4	9	13
	hypotension	54	59	78
Total		100	99	199

What does the pertinent literature reveal?

Incidence and disease onset: Are there differences between the sexes? Males suffer from Parkinson's syndrome more than women do. In 2000 Baldereschi and coworkers reported an incidence two times higher in men than in women [7]. Admittedly, in an extensive metaanalysis, Wooten and coworkers found a slightly smaller incidence rate for male patients, but the risk of contracting Parkinson's was still 1.5 times higher for men compared to women [8]. The imbalance was thus still in favor of the women. Georgiev and coworkers analyzed patient data for the period of 1990 until 2016 and identified a larger accumulation for males than for females. They also showed that in the course of the disease the symptoms occurred earlier in the men [9]. The analysis of a small cohort of 253 patients gives support to these observations: Haaxma and coworkers found that the women received their initial diagnosis on the average two years later than the men [10]. On

the other hand, Baba and coworkers could not confirm any demographic differences concerning disease outset in their study population of over 1,200 patients [11]. An analysis of 1,741 US-American patients also could not find any differences (1) in disease outset of men compared to that of women or (2) in the time interval between the inaugural symptom and the date of the official diagnose [12]. The same finding was given in an analysis of 681 Spanish patients [13].The findings to date establish a tendency for more men to contract the disease than women, but it appears improbable that any other demographic difference exists, although it cannot be reliably ruled out at the present.

Table 8. Motor and non-motor symptoms

Author		Symptom	Women	Men
Liu 2015	cross sectional analysis n=414	Tremor	-	+
Solla 2012	observational study n=156		+	-
Georgiev 2017	meta-analysis 1990-2016		+	-
Georgiev 2017	meta-analysis 1990-2016	Rigor	-	+
Liu 2015	cross sectional analysis n=414 Pat		-	+
Santos-Garcia 2013	cross-sectional analysis n=681		-	+
Baba 2005	Comparative study n=1264		-	+
Liu 2015	cross sectional analysis n=414	Bradykinesia	-	+
Liu 2015	cross sectional analysis n=414	Postural instability	Almost identical	
Colombo 2015	observational study n=617	Postural instability, unsteady gait, wearing off	+	-
Kim 2018	retrospektive n=390	Freezing	+	Occurs rather later
Ou 2018	prospective study n=263	Camptocormia	-	+
Chou 2017	observational study n=728	Falls	+	Increase as of age 70
Parashos 2018	data analysis n=3795		+	-
Gao 2022	observational study n=200	Pain	+	-
Silverdale 2018	Clinical study n=1957		+	-
Santos-Garcia 2013	cross-sectional analysis n=681		+	-
Nienstedt 2019	cross sectional, observational analysis n=119	Dysphagia	+	-
Nienstedt 2019	cross sectional, observational analysis n=119	Sialorrhea	-	+
Broen 2018	cross-sectional analysis n=311	Anxiety, depression	+	-
Wissel 2018	data analysis n=53		+	-
Rodriguez-Blazquez 2020	cross-sectional study n=402	Depression	+	-
Martinez-Martin 2012	observational analysis n=951	Depression	+	-
Santos-Garcia 2013	cross-sectional analysis Follow up n=681	Fatigue, depression	+	-
Picolli 2013	observational analysis n=200	Depression	=	=
Weintraub 2010	cross sectional study n= 3090	gambling addiction, hypersexuality	-	+
Santos-Garcia 2013	cross-sectional analysis Follow up n=681	Hypersexuality	-	+
Kon 2018	retrospektive analysis n=148	Disorders of impulse control	-	+
Cholerton 2018	observational study n=418	Mild Cognitve Impairment	-	+
Szewczyk-Krolikowski 2014	observational study n=490 comparison group n=176		-	+
Nicoletti 2017	multicenter case control study n=585	Non-motor symptoms	-	+
Accolla 2007	observational study (DBS) n=38	Dyskinesia	+	-
Baba 2005	comparative study n=1264		+	-
Zappia 2005	cohort study n=250	Peak-dose-dyskinesia	+	-
Santos-Garcia 2013	cross-sectional analysis Follow up n=681	Levodopa total dose	-	+
Baba 2005	comparative study n=1264		-	+

Motor and non-motor symptoms

The symptoms that are recognized as being pathognomonic for Parkinson's (rigor, tremor, bradykinesia) can of course be found in both male and female patients, but on this issue there are discrepancies and incomplete data in the current literature. Motor symptoms appear to be less severe in women compared to men (n=415) [14]. These rather more mild symptoms in female patients are reflected in the lower number of points given in the UPDRS Motor Score (n=415) [15]. However, female patients complain more about lower quality of life than male patients do. Fatigue and depression may very well be contributing factors here [16]. While Solla and coworkers found more tremor among females in their sample of 156 Sardinian patients [17], Liu and coworkers identified more tendency for tremor among men in a larger cohort [18] Postural instability belongs to the most obvious of symptoms in the disease, and is characterized by the inability to maintain balance under either static or dynamic conditions [19]. Up to now, the symptom has been attributed to later, more advanced stages of the disease, but Pérez-Sánchez and coworkers have doubts whether this holds true categorically: They describe instances in which this symptom has very well been observed in early stages of idiopathic Parkinson's [20], but it remains to be seen whether their observations can be confirmed in further studies. Our present discussion here clearly shows that there are still a good many basic questions that have to be solved in Parkinson's syndrome. This situation might cause a certain amount of consternation and poses the question of just how fundamental our present-day knowledge is to be considered valid knowledge, or, vice versa, how many new ideas can shake up our idea of the fundament? How much do we actually know about the disease? And so, a challenging question is just how much we actually know about the disease. Assigning the symptom of postural instability to just one sex has just simply not been conclusively resolved. The studies from Liu and Colombo, from the same year of publication, appear to confirm the doubts since their results are so dissimilar [21].The topic of sex and gender aspects in idiopathic Parkinson has been the subject of study, analysis and discussion for some time now, but we are still far off from any consensus whatsoever. In a retrospective analysis in 2018, Kim and coworkers came to the conclusion that freezing occurred in women somewhat earlier in the course of the disease than in men [22]. On the other hand, Ou and coworkers found camptocormia to occur earlier in male patients than in females [23]. In two extensive data analyses [24,25] the authors, independently of each other, reached the conclusion that falling events occur more often in women. Chou and coworkers found a larger number of falls in male patients after the age of 70. Work by Accolla and coworkers and by Zappia and coworkers [26,27] found dyskinesias to occur more frequently in their female patients. The results from Gao and coworkers [28] and from Silverdale and coworkers [29] show a similar picture: They addressed the theme of pain in idiopathic Parkinson's, a frequent complaint that does not often receive the appropriate attention, although it clearly impacts the quality of life in afflicted patients. The causes of pain are usually multifactorial [30]. Goa and coworkers analyzed the data of 200 patients, Silverdale and coworkers did the same for 1,957 patients. Both studies came to the conclusion that pains were more often diagnosed in female patients and the same was true for anxiety and depression. These neuropsychiatric symptoms appear more often attributed to the female sex [31,32].

Impulse control disorders, which occur more often under medication with dopamine agonists, were observed occurring more often in male than female patients [33,34]. Likewise, cognitive deficits (mild cognitive impairment) have been attributed more to male gender: This was shown in two smaller studies from 2014 and 2018 [35,36]. In addition, one multicenter study with 585 patients analysed the occurrence of non-motor symptoms in men and women with Parkinson's: The women had a higher rate of depression and bladder dysfunction, whereas men generally had significantly more non-motor symptoms [37]. Rodriguez-Blazquez and coworkers [38,39] also came to the conclusion that depression occurs more frequently in the women patients: They also examined non-motor fluctuations and described for their collective a rate of 41%. A sex-specific difference was not observed in their data [40]. During earlier stage of the disease there is rather no difference in the occurrence of depressive symptoms between the sexes [40]. Furthermore, women in the prodromal phase of the disease may experience not only the known prodromal symptoms but also a subjective sense of cognitive decline also presaging the later outbreak of the disease [41]. A further study on non-motor fluctuations [42] likewise found essentially more such fluctuations in the female patients.

On the occurrence of motor and non-motor symptoms within the different sexes, the available studies currently show selective conformities, but just as well discrepancies. What is thus yet missing is a solid, reliable basis to draw final conclusions on sex and gender-associated criteria. Relying on a review of the literature to date, Cerri and coworkers attempted a preliminary description of the "typical" male and the "typical" female Parkinson patient [43]. This approach is indeed intriguing, although a reliable fundament is missing, and thus intensive discussion and targeted studies are much needed in the future (Table 8).

The role of neurosteroids

The general agreement on men being more often afflicted with Parkinson's than women brings up the question of the possible causes. Different hypotheses are being discussed here: Genetic dispositions and sex-specific metabolic processes could be playing a role, as well as gender-associated risk factors. Among these latter factors are, for example, a higher incidence of traumatic brain injury and also a statistically increased exposure to harmful substances in men [8].

In recent discussions, the observation that women have a lower level of incidence and less-pronounced symptoms at outset suggests a possible correlation with the estrogen status [44]. The duration of the estrogen exposition could possibly be associated with the reduced incidence in women. In spite of the fact that the study from Benedetti and coworkers failed to achieve statistical significance, they took this hypothesis into consideration [45]. Since then this estrogen hypothesis has been subject to considerable discussion and a number of studies have specifically examined the effect of pharmacologically applied estrogen on Parkinson patients [46,47].The assumption here is that estrogens could be activating a neuroprotective effect in astrocytes. While estrogen is preferentially seen as having a neuroprotective effect, male testosterone might possibly have a negative effect on the course of the disease [48]. In a review from 2016 Villa and coworkers already outlined potential neuroprotective effects of estrogen and drew the preliminary conclusion that premenopausal women have a reduced risk for Parkinson's [49]. This would hint at the idea that the course of neurodegenerative diseases such as Parkinson's or Alzheimer's might be positively influenced through estrogens. A few studies point in this direction [50], so that hopes of treatment with the use of estrogen substitution have been raised [51]. Using information from a survey of patients by the Michael J. Fox Foundation, Mathur and coworkers analyzed the data of more than 2,600 women with Parkinson's. Their focus was on the personal self-image of the afflicted women. 61% of the participants indicated that they had a negative self-image due to the disease. In their conclusion, the authors identified a greater risk for depression and mental disorders in the women [52]. A further aspect of their analysis addressed the age factor and the resultant hormone status of the women in pre, peri and post-menstrual stages. Altogether, they examined 18 categories including weight, motor behavior, speech, disturbance in bladder functions, sialorrhea and bodily appearance. The results supported the suggestion that there is in fact an association between hormonal status and the estrogen hypothesis mentioned above. But, given the current status of research, the actual relevance of estrogen and its potential therapeutic effect remain uncertain.

In a review, Tansey and coworkers directly addressed the pathophysiology of the disease: They in no way doubted the prevailing view of the pathophysiology in Parkinson's disease that the neurodegenerative processes stem from misfolded proteins which accumulate within neurones as so-called Lewy bodies. They consider the possibility that immunological processes might possibly be implicated in the etiology of the disease [53].

This then re-focuses attention on so-called neuroactive steroids, specifically steroids produced in neurones, glia cells and endocrine glands, including estrogen, testosterone and progesterone and their metabolites. The aspects of particular concern here would include the positive, immune-modulating effect of progesterone in the course of ovulation [54], which could possibly be associated with the reduced incidence of Parkinson's disease in women. Experimental work, including animal models of the disease, has succeeded in demonstrating neuroprotective and anti-inflammatory effects [55]. If positive effects do accrue to estrogen, the question comes up as to whether the masculine hormone testosterone possibly might have a major influence, of whatever kind, but the current status of our research is inconclusive here. A few, smaller studies, usually dating back considerably, have postulated that men afflicted with Parkinson's have a demonstrably lower blood level of testosterone compared to healthy cohorts of similar age [56]. One topic which by far has not been conclusively clarified in its relevancy for Parkinson's is the role of a receptor expressed in the pars compacta of the substantia nigra: The retinoic acid receptor-related orphan receptor alpha-RORA. Since the role of RORA has become the subject of extensive scientific research over recent years in such disorders as the autism spectrum (which also show clear differences in the sexes) [57], its relevancy for Parkinson's disease has been given considerable attention. RORA has been attributed with a neuroprotective efficacy, and, because its expression is regulated by sexual hormones, the receptor might very well constitute an important mosaic stone for solving questions of sex differences in Parkinson's. Al-Zaid and coworkers highlighted this issue in a study on human brains postmortem. Interestingly he did the first study that succeeded in showing, at least *in vitro*, a profit in the form of neuroprotection through use of RORA agonists. This is clearly a ´very promising approach which will provoke further work along this line [58].

The relevancy of genetics

In general, gene expression on either the X or the Y chromosome is decisive for a person's predisposition to diseases and its course. Technological advances in gene sequencing and genetic typing over recent years have provided major new findings for our understanding of basic genetics for the idiopathic and the genetically determined Parkinson's disease. For this genetically determined disease, altogether 20 gene variations have been identified by now as risk factors, and for sporadic Parkinson's 90 variants have so far been tagged as such. Their possible effects on the organism are numerous and have effects all the way up into signal-transduction pathways [15]. Parkinson's disease in women is apparently associated with a modified variant of the gene coding for glucocerebrosidase (GBA) [59]. The GBA variant as well as the LRRK2 gene (leucine-rich repeat kinase 2) have both been examined comparatively well. Several studies suggest that mutations of this gene may have relevancy in Parkinson's in females. The LRRK2 G2385R variant has been implicated in the sex-related extent of motor and non-motor symptoms, for example: Cui and coworkers directly associated the LRRK2 variant in explaining that women patients show fewer reductions in everyday activities, present with fewer autonomic dysfunctions and have fewer affective disorders than male patients [60]. A further role was possibly identified for the G2019S subgroup which has a higher incidence in women than men [61,62]. Pelzer and coworkers showed that three subgroups of the dopamine receptor D (2) DRD2 Taq1A (rs1800497) occurred at different frequencies between the sexes [63], and were associated with differences in responsivity to levodopa. But it has not yet been clarified as to whether concrete symptoms are in fact associated with all the identified gene loci or just which mechanisms are playing a role here. But there are preliminary indications confirming a sexual differentiation along these lines. Confirmation has recently been found connecting changes in the ANKK1 (dopamine receptor D (2) (DRD2)/ANKK1) and BDNF (brain-derived neurotro-phic factor) gene loci with levodopa-induced dyskinesias (LiD) [64]. In addition, female sex, early onset of the disease and anxiety disorders were found to be risk factors for LID [65]. Likewise, a number of gene types of the dopamine receptors have been identified as risk factors for the development of impulse control disorders [66]. Since males suffer from this symptom complex more than females, it would be very advantageous if we could find out whether the gene types under discussion are in fact less often expressed in women.

Discussion and Conclusion

Our analysis of the data from 100 male and 100 female hospitalized Parkinson patients shows that the majority of the women became ill somewhat later than the men did and that they were being treated with a lower dosage. We found a further significant distinction in the frequency of the diagnosis depression which was more frequently given for female patients. It would, however, be premature to attribute that merely to the primary disease, Parkinson's, as depression is diagnosed even in otherwise healthy men less often. As a result sociocultural differences, that is, gender aspects cannot be ignored and the association between women, the more frequent diagnosis of depression and Parkinson's has to be discussed with caution. Interestingly, although the empirical literature to date associates rigor and tremor more frequently with male sex, our data does not find corroboration for this difference. We are likewise somewhat critical on our finding of a lower equivalence dose for women: It is standard clinical practice to take both the patients' sex and weight into consideration in determining the levodopa total dose which automatically entails a lower dose for females patients. That men more often contract Parkinson's is indisputable today, and there are some indications that their symptoms are not identical with those of female patients. However, the present status of research is inconsistent and is in need of further detailed work directly addressing the topic.

The gold standard in medical treatment is still levodopa. For so-called late complications such dyskinesias, a strong levodopa daily dose and female sex can be viewed as a risk factor, and such a factor would strongly suggest sex-specific levodopa dosages. Here further studies are necessary. In the present state of our studies, we still do not know to what extent neuroactive steroids influence the pathophysiology of the disease and what their therapeutic use would effect. There is thus a crucial need for targeted, prospective and longitudinal studies which analyse the data from females, males and trans-gender persons with Parkinson's disease separately. In clinical routine work the awareness has to be improved on for the different genders whose course of the disease, symptoms and responsivity to medication can very well be substantially different: We will only be able to perceive and appreciate what we have already conceptualized in our minds.

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None.

Conflict of Interest

The authors declared no conflict of interest.

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