

## OTHELLO SYNDROME IN PATIENTS WITH PARKINSON'S DISEASE

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### SUMMARY

**Background:** Othello syndrome (OS) is an organic delusional disorder with prevailing jealousy symptoms presumably appearing as side effect of antiparkinsonian therapy. The clinical spectrum of psychiatric symptoms in Parkinson's disease (PD) is very wide, including symptoms of depression and anxiety, hallucinations, delusions, with prevalent paranoid symptoms, agitation, delirium and sleep disorders. At our knowledge, just a few cases of patients with PD and OS were reported till now.

**Methods:** three neurologists working in a tertiary referral centre were asked to report cases of pathological jealousy as defined by the DSM IV criteria (Kaplan et al. 1994). The following data were collected retrospectively: sex, age at PD onset, age at OS onset, duration of PD, duration of PD treatment, duration of treatment with dopamine agonists (DAs), treatment of OS, past history of alcoholism, premorbid personality disorder, family history of psychiatric disorders and data about general cognitive condition.

**Results:** Five PD patients (three males) with OS were investigated. The mean age of the patients at the PD onset was  $46.80 \pm 8.87$  (SD), the mean age at the OS onset was  $56.40 \pm 8.76$  (SD). Before the onset of OS, all of them were taking dopamine agonists. The first patient was treated with pramipexole, apomorphine infusion and levodopa/carbidopa, the second with apomorphine infusion plus levodopa/carbidopa/entacapone, the third with pramipexole, the fourth and fifth with ropinirole. Decrease of dopamine agonist led to clinical improvement in three patients (complete reduction of the symptoms in two, reduction of symptoms in one patients). In two patients, the symptoms remained the same. In three patients atypical neuroleptics had to be added: clozapine in two and quetiapine in one patient.

**Conclusions:** We believe that OS is a more common psychiatric side effect in PD patients on treatment with dopamine agonists than usually believed, particularly in those with early disease onset. It is a very disturbing symptom for patients and their partners, often underestimated by them, and should therefore be actively searched for.

**Key words:** Othello syndrome - delusional jealousy - Parkinson's disease - dopamine agonists - atypical neuroleptics

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### INTRODUCTION

Dopamine receptor agonists (DAs) are effective treatment option for Parkinson's disease (PD). In the the early stage PD they can be used alone, whereas in the late stage PD they are used as adjunctive therapy, together with levodopa (LD) (Bonuccelli & Pavese 2006). In some patients they have been shown to be as effective as LD in symptomatic treatment of mild-to-moderate PD (Tintner & Jankovic 2003). In addition, there is a lower tendency to develop motor fluctuations and dyskinesias with DAs treatment than after initiation of therapy with LD. Furthermore, some preclinical and clinical data suggest slowing of neurodegeneration with Das (Tintner & Jankovic 2003). However, besides their good efficacy in the treatment of PD, the use of DAs is associated with many adverse effects as well. Recently, impulse control disorders and aberrant repetitive behaviours have surged to clinical relevance as they occur during dopamine replacement treatment (mainly with dopamine agonists) and worsen patients' and caregivers' quality of life (Antonini & Cilia 2009). Moreover, a study showed that these disorders are found in patients taking therapeutic doses of dopamine agonists but was not found among untreated patients, those taking

subtherapeutic agonist doses, or those taking carbidopa/levodopa alone. (Bostwick et al. 2009). Besides this, the use of DAs has been shown to be the most widely identified risk factor for PD psychosis. (Zahodne & Fernandez 2009). Some studies showed that up to 25% of PD patients suffer from delusions and hallucinations (Fenelon et al. 2000). The clinical manifestation of psychosis in PD patients is very diverse. It ranges from minor symptoms of mild illusions, vivid dreams, and occasional, non-disturbing visual hallucinations to a frank psychosis with confusion, disturbing visual (and, rarely auditory and tactile) hallucinations, and persecutory delusions (Thanvi et al. 2005). In idiopathic PD, psychotic symptoms are usually induced by dopaminomimetic agents or cholinergic antagonists and are also associated with age, disease stage, depression and cognitive impairment, but not with clinical subtype, disease duration or dose of dopamine agonists (Aarsland et al. 1999, Giladi et al. 2000). Othello syndrome - OS is defined as a false belief derived from delusional jealousy that one's lover is unfaithful (Kaplan et al. 1994). It is a delusion supported by the absolute certainty of the infidelity of the partner. It is also considered to be one of the manifestations of dopamine dysregulation syndrome (Evans & Lees 2004). OS is common among

chronic male alcoholics. It was also described in a context of other different functional and organic psychiatric and neurologic conditions. As a part of functional psychotic disorder, it was described in schizophrenia, delusional, affective and personality disorders and neurosis (Cannas et al. 2009). In the context of general medical disorders, it has been reported in dementia (Tsai et al. 1997), cerebrovascular infarction (Luaute et al. 2008), hyperthyroidism (Hodgson et al. 1992) and normotensive hydrocephalus (Yusim et al. 2008). It was also reported after right orbitofrontal excision after an operation for tuberculoma sixteen years before the appearance of the syndrome (Narumoto et al. 2006). At our knowledge, just a few cases of OS in the context of PD were reported till now (Cannas et al. 2009, Brüne et al. 2007, Mc Namara & Dusro 1991). We report five patients with OS undergoing dopaminergic treatment. Because data in the literature suggest high prevalence of delusional jealousy in the context of dementia and chronic alcoholism, patients with cognitive decline and history of alcoholism were excluded from the study. The aim of the paper is to draw attention to this syndrome as a condition that is more frequently seen in patients with PD on DAs than usually believed. In addition, because of its disturbing and even dangerous nature for the patients and their partners, it should be particularly taken into account when taking the follow-up history and tailoring the treatment protocol.

## METHODS

Three neurologists working in a tertiary referral centre were asked to report cases of pathological jealousy as defined by the DSM IV criteria (Kaplan et al. 1994). The following data were collected retrospectively: sex, age at PD onset, age at OS onset, duration of PD, duration of PD treatment, duration of treatment with DAs, treatment of OS, past history of alcoholism, premorbid personality disorder, family history of mental disorders and data about general cognitive condition. Additional data (data not explicitly written in the histories, current state of the patients) were collected by contacting the patients and/or their spouses.

## RESULTS

Five patients (two females, three males) were reported. The mean age of the patients at the PD onset was  $46.80 \pm 8.87$  (SD), whereas the mean age at OS onset was  $56.40 \pm 8.76$  (SD) years. The mean

duration of PD before the OS onset was  $10.80 \pm 9.41$  (SD). The mean duration of PD treatment was  $10.00 \pm 9.33$  (SD) years. The mean duration of DAs treatment was approximately six years ( $6.25 \pm 4.72$  (SD)) (Table 1). Mean age of the patients when the therapy with DAs was introduced was  $52.80 \pm 6.98$  years. The mean period when symptoms were first recognized by the patient and the diagnosis of OS by a medical professional was  $4 \pm 4.06$  (SD) months. None of the reported patients had obvious cognitive decline. The past history was negative for chronic alcoholism and premorbid personality disorder, as was the family history for mental disorders in all patients. However, four of five of them had already shown features of jealous behavior before the introduction of DAs. Four of the patients had typical persecutory and jealousy delusions, whereas one had delusional disorder with predominant jealous symptomatology and delirious episodes. Two of them had osmic hallucinations (Table 2).

**Table 1.** Demographic and clinical data (PD=Parkinson's disease; OS=Othello syndrome; DA=Dopamine Agonists)

Sex	2 females and 3 males
Mean age at PD onset*	$46.80 \pm 8.87$ (SD)
Mean age at OS onset*	$56.40 \pm 8.76$ (SD)
Mean duration of PD*	$10.80 \pm 9.41$ (SD)
Mean duration of PD Rx*	$10.00 \pm 9.33$ (SD)
Mean age at DA Rx start*	$52.80 \pm 6.98$ (SD)
Mean duration of DA Rx*	$6.25 \pm 4.72$ (SD)

\*data in years

The influence of the OS on the everyday living at the beginning and at the last evaluation in 2009 is shown in table 3. At the OS onset, two of the patients were on continuous dopaminergic treatment with apomorphine. One of them, besides apomorphine, additionally had pramipexole and a combination of Levodopa/Carbidopa in the therapy, the other in addition to apomorphine had Levodopa/Carbidopa/Entacapone combination. The third patient was only on pramipexole, and the fourth and fifth had only ropinirole in the therapy. The common therapeutic procedure for the treatment of OS in all patients was reduction of the DAs dose (in one of the patients the therapy with ropinirole was actually abolished). In three patients atypical neuroleptics had to be added: clozapine in two and quetiapine in one. In one case, a reduction of the symptoms was achieved, in two cases delusional symptomatology disappeared, whereas in two cases no improvement of the condition was achieved (Table 4).

**Table 2.** Descriptive symptomatology

1 <sup>st</sup> patient	2 <sup>nd</sup> patient	3 <sup>rd</sup> patient	4 <sup>th</sup> patient	5 <sup>th</sup> patient
Delusional disorder with predominant jealous symptomatology;	Persecutory and jealous delusions	Persecutory and jealous delusions	Persecutory and jealous delusions;	Persecutory and jealous delusions
Deliriant episodes;			Osmic hallucinations	
Osmic hallucinations				

**Table 3.** Influence of OS on the daily activity of the patients (OS=Othello syndrome)

	1 <sup>st</sup> patient	2 <sup>nd</sup> patient	3 <sup>rd</sup> patient	4 <sup>th</sup> patient	5 <sup>th</sup> patient
Upon dg. OS	+++	++	+++	+++	+++
2009	+	/	+	+	0

0 – without influence; + - mild influence; ++ - moderate influence; +++ - strong influence; / - no data available

**Table 4.** Treatment profile (OS=Othello syndrome, DA=Dopamine Agonists)

	1 <sup>st</sup> patient	2 <sup>nd</sup> patient	3 <sup>rd</sup> patient	4 <sup>th</sup> patient	5 <sup>th</sup> patient
Treatment at the onset of OS	apomorphine infusion pump; pramipexole; levodopa/ carbidopa	Apomorphine infusion pump; levodopa/ carbidopa/ entacapone	pramipexole	ropinirole	ropinirole
Treatment of OS	DA decrease; clozapine, quetiapine	DA decrease; quetiapine	DA decrease	DA decrease clozapine	DA abolition
Maximal dose of atypical neuroleptics used/24h	clozapine (50 mg) quetiapine (400 mg)	quetiapine (225 mg)		clozapine (75 mg)	
Outcome	Reduction of symptoms	No impv't after DA decrease and Rx with quetiapine	Disappearing of symptoms	No impv't after DA decrease and Rx with Clozapine	Disappearing of symptoms

## DISCUSSION

Psychotic symptomatology in PD is variable. It is thought to have a bimodal onset. The early onset psychotic manifestations occur in the first few years of the disease evolution, associated with motor fluctuations and large doses of drugs later on during the disease progression. The late onset psychotic manifestations are associated with cognitive impairment (Thanvi et al. 2005, Danieli et al. 2004). The central pathological feature of PD is degeneration of dopamine-producing cells, not only in the substantia nigra (SN), but also in the ventral tegmental area of the midbrain (VTM). The degeneration of dopaminergic cells leads to reduction of dopamine in key projection areas of nigrostriatal and mesocorticolimbic projections (Wolters & Berendese 2001). The former leads to abnormal motor behavior, the clinical hallmark of PD (tremor, rigidity, bradykinesia, postural insta-

bility). The latter, however, leads to abnormal mentation: psychomotor retardation with hedonistic homeostatic regulation, anxiety or depression and cognitive dysfunction possibly resulting in overt dementia later on during the disease progression (Giovannoni G, Cantello R.). A reduction of mesocortical dopaminergic activity may be inversely related to mesolimbic dopaminergic activity, which could be an effect of serotonin-modulated GABAergic neurons, that stimulate dopaminergic neurons in VTA, but not the dopaminergic neurons in the parabrachial nucleus, that projects to the prefrontal cortex (Wolters & Berendese 2001). The limbic dopaminergic loop connects the inferior prefrontal cortex, nucleus accumbens, ventral pallidum, medio-dorsal nucleus of thalamus and inferior frontal cortex, and it is, among other things, concerned with visual expression of emotions. ClarkThe dopaminergic excitation of the limbic region with reduced

prefrontal stimulation might cause sensory input from multiple association cortices to be misinterpreted, which in turn leads to delusions and hallucinations (Wolters & Berendese 2001). In addition to the dopaminergic deficit, degeneration of the cholinergic, noradrenergic and serotonergic systems seem to be important in the pathogenesis of the cognitive impairment in PD patients. Moreover, in demented PD patients, delusions and hallucinations might be caused by the cholinergic deficit itself (Wolters & Berendese 2001). Patients with PD with OS exhibit particular characteristics compared to patients with OS due to treatment different aetiology. All patients presented in this paper were middle-aged, they were cognitively well, all of them were taking DAs for several years before the OS onset (mean age at DAs introduction was  $52.80 \pm 6.98$ , mean age of OS onset was  $56.40 \pm 8.76$  years) and none of the patients consumed excessive amounts of alcohol. The critical event was probably introduction of DAs or increment of the dose, although four of the patient had already had signs of jealous behavior before the introduction of DAs. This is in accordance with the data published earlier (Cannas et al. 2009). Quality of life, as assessed by the patient themselves, was markedly diminished in all patient at the OS onset. Following the treatment few years after the OS onset, the quality of life improved in all patient, as could be seen in the table 3. We additionally noticed one peculiar characteristic in two patients in our group, namely osmic hallucinations. This is in contrast to frequently reported visual hallucinations in PD, and might be a result of the pathological changes in the olfactory bulb in patients with PD (Wolters & Berendese 2001, Thanvi et al. 2005). This, may be somehow associated with the olfactory pathology, which is prominent even in the presymptomatic stages of PD (Braak et al. 2004). OS could also be considered to be a monosymptomatic expression of psychosis uncovered by DAs in PB. This is further supported by the fact that two of our patients did not improve delusional symptomatology on the treatment provided. Although it is true that all dopaminergic drugs, have the potential of inducing OS and probably other psychotic reactions, we believe that this effect is especially pronounced with the use of DAs. All patients in the present study were treated with DAs at the OS onset. Therapeutical approach to OS in PD patients remains undefined and deserves attention as well. In all patients the DA dose was reduced, in one case DA was even abolished. As a further step, atypical antipsychotics should be used in the

treatment of OS. They are also used to treat other psychotic events in PD and in parkinsonism in general. The atypical antipsychotics are not only antagonists to the dopaminergic (D2) receptors, but also to serotonergic, muscarinic, cholinergic, adrenergic and histaminergic receptors. They have a low propensity for inducing extrapyramidal symptoms, and are therefore preferred over the typical neuroleptics, as haloperidol. We treated our patients with clozapine and quetiapine, which are generally most commonly used atypical antipsychotics in patients with parkinsonism. It is also important to mention that the mean period when symptoms were first recognized by the patient and the diagnosis of OS by a medical professional was approximately 4 months, which indicates that the OS could be easily recognized as exaggerated behavioral change by the patients and/or their spouses, which in turn would force them to consult physician, who could confirm the diagnosis.

## CONCLUSION

OS in PD patients may be more common than reported and may preferentially affect patients with young onset PD, who already show jealous traits, particularly those receiving DAs, who may be at special risk. Although usually disturbing symptom for the patients and their partners, it is largely underestimated and may be relatively resistant to treatment. Symptomatology of OS should therefore be actively searched from the partner, as well as from the patient. A comprehensive explanation and modification of treatment as well as the use of atypical antipsychotics should be offered to the patients and their family.

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