Conjugal Parkinson´s disease – real or chance?

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Sir,

We read with great interest the publication by Rajput and colleagues, reporting the autopsy findings of five couples with conjugal parkinsonism (including three with atypical parkinsonism like multisystem atrophy (MSA) or progressive supranuclear palsy (PSP), but only two with Parkinson´s disease) and concluding that neither a prion-like transmission nor shared environmental factor seem to play a role in the pathogenesis of Parkinson´s disease.[1]They further suggest that the risk of parkinsonism in unrelated couples is similar to that in the general population.

Here we present our own data and also a literature review, and suggest that the above conclusions may be premature and prospective large cohort studies are needed. Parkinson´s disease (PD) is characterised by α-synuclein accumulation with a prevalence rate in the UK population >65 years of 12.1/1000. Environmental factors have been continuously implicated in its pathogenesis, whereas current interest focuses on the gut-brain axis and on the so-called *prion-hypothesis* of α-synuclein spread. There is accumulating evidence suggesting that α-synuclein may be responsible for initiating PD, and that its spreading is associated with disease progression.
α-synuclein is present in saliva and plasma of PD patients, and has been shown in animal models to be taken up and transferred by neurons. In prion disease itself, body fluids like saliva are considered to be of low infective risk. Thus, the question arose if conjugal PD is a chance finding or indicative of PD could being a communicable, prion-like disease.
In this light we would like to present the two couples with conjugal PD amongst our cohort of 160 PD patients and discuss the implications of this finding.

Couple_#1 (*video*): This 79-year-old man has been carer of his 77-year-old wife, diagnosed with PD 15 years earlier. They have been together for 55 years and reported residential, non-occupational pesticide exposure. When he accompanied her to our clinic, he mentioned having slowed down lately. He had lost his sense of smell for several years and, more recently, had developed dream enactment. On examination, he had hypomimia and asymmetric bradykinesia. A DaTSCAN was abnormal.
Couple_#2: This 80-year-old man has been taking care of his wife, affected with PD for five years. They had been married for 40 years. Six months ago, she noted a tremor of his jaw and his leg. In the past, he has had dream enactment. On examination, he had hypomimia, rest tremor, bradykinesia and rigidity of the left arm and leg. His gait was small stepped. A DaTSCAN was abnormal.
None of the patients had consanguineous parents or a family history of PD.

Based on aforementioned prevalence rates, the chance of two spouses having PD would be 0.014% in the general population. Thus, the point prevalence of conjugal PD in our sample (1.25%; 95% CI: [-0.47;2.97]) exceeds the expected prevalence by far and implies a risk ratio of 83.33 (95% CI 19.21;361.440). The conjugal occurrence of α-synucleinopathies has been previously noted (table), yet mostly without putting these observations into the context of prevalence rates. Most case-control studies in PD did not systematically assess spouses for PD. Those reporting no cases of conjugal PD had some methodological limitations in this regard, like assessment by questionnaire only, or small sample size.[2,3] Two studies, however, documented increased conjugal PD/parkinsonism rates of 0.43% and 0.48%, respectively, despite a study design not targeting sensitive detection of such cases.[4,5] Besides, such figures may be an underestimate considering that some included patients may have been single. Our observation shares some limitations with previous reports, including the small sample size. This is reflected by large CIs, indicating low accuracy. Yet, a risk ratio of about 20 (inferior limit) would still appear impressive. However, such statistics critically depend on the theorem of large numbers, which we acknowledge is a limitation here.

Thus, the question remains if conjugal PD is a real or a chance finding.

Rajput and colleagues[1] argue that in conjugal parkinsonism, both partners should have the same pathological phenotype if the disorder was transmittable or caused by shared environmental risk factors. Thus, the pathological discordance of some of their couples (e.g. MSA and PD; PSP and tauopathy with features of PSP and CBD) would refute such hypotheses. However, probably it can't be excluded that individual predisposition might modify the clinical and pathological phenotype.

We feel before assuming definite conclusion, a systematic approach with large cohorts would be required to re-appraise this matter, which has important implications.

Publication	**Main findings**
Ramani M, Saur DP, Rabin M, Kurlan R. Conjugal and familial Lewy body disorders: a report of one family. Parkinsonism Relat Disord. 013;19(4):498.	1 couple Husband PD, onset age 64 years Wife DLB, onset age 61 years Shared environmental risk factors: > 30 years history of wellwater intake; molybdenum mined in their residential county Family history: PD (husband´s sister)
Willis AW, Sterling C, Racette BA. Conjugal Parkinsonism and Parkinson disease: a case series with environmental risk factor analysis. Parkinsonism Relat Disord. 010;16(3):163-6.	9 couples (PD/PD) recruited between 1994-2005 Duration of cohabitation prior to symptom onset in the firstly affected spouse: average 39.9 years (±9.2) *(in our cases: 35 and 40 years)* Time to disease onset in the second spouse average 4-9 years, range 1-13 years *(in our cases: 5 and 15 years)* Shared environmental risk factors: residential, non-occupational pesticide and heavy metal exposure in 77.8% (7/9) of couples *(in our cases: residential, non-occupational pesticide use (gardening) in couple #1)*
Miwa H, Kondo T. Conjugal parkinsonism: multiple system atrophy and Parkinson's disease. Parkinsonism Relat Disord. 010;16(3):232.	1 couple Wife: PD, onset 62 years Husband: multisystem atrophy Shared environmental risk factors: parathion use for gardening for 10 yrs
Counihan TJ. Conjugal Parkinson's disease. Lancet. 2003;361(9353):252.	1 couple (PD/PD) no further details
Strang RR. Conjugal parkinsonism. Dis	2 couples (PD/PD) observed in 897 cases of PD (bachelors excluded)

Nerv Syst. 1967;28(12):814-5.	*(corresponding to a prevalence rate of 0.22%)*	
	Age at onset 57 years (range, 55- 61 years)	

Table: Overview of previously reported cases of conjugal α-synucleinopathies.

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Web resources:

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Supplementary material: Video.

The video shows couple 1. He has hypomimia, reduced arm swing, reduced shoulder shrug and bradykinesia (left more than right). She has classic levodopa-induced, generalised dyskinesia, hypomimia, reduced shoulder shrug on the left more than on the right, and a subtle rest tremor on the left.

Author contributions:
Dr. Balint - Study concept and design, acquisition of data, analysis and interpretation, writing the first draft, critical revision
Dr. Erro - analysis and interpretation, critical revision of the manuscript for important intellectual content
Dr. Brugger - acquisition of data, critical revision of the manuscript for important intellectual content
Dr. Jha - critical revision of the manuscript for important intellectual content
Dr. Batla - critical revision of the manuscript for important intellectual content
Dr. Ganos - critical revision of the manuscript for important intellectual content
Dr. Antelmi- critical revision of the manuscript for important intellectual content
Prof. Bhatia - Study concept and study supervision, critical revision of the manuscript for important intellectual content

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