Parkinsonism and Related Disorders 31 (2016) 87–90

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Conjugal parkinsonism – Clinical, pathology and genetic study. No evidence of person-to-person transmission

Ali H. Rajput [a, *], Leslie W. Ferguson [a], Christopher A. Robinson [b], Ilaria Guella [c], Matthew J. Farrer [c], Alexander Rajput [a]

[a] Saskatchewan Movement Disorders Program, University of Saskatchewan/Saskatoon Health Region, Canada
[b] Division of Neuropathology, Department of Pathology, Saskatoon Health Region, Canada
[c] Centre of Applied Neurogenetics, University of British Columbia, Canada

ARTICLE INFO

Article history:
Received 30 May 2016
Received in revised form
15 July 2016
Accepted 22 July 2016

Keywords:
Parkinson syndrome
Autopsy
Conjugal
Transmission
Environment

ABSTRACT

Introduction: Neurodegeneration is known basis of several different Parkinson syndromes. The most common Parkinson syndrome is the Parkinson's disease. Distinction between different Parkinson syndromes is based on pathology or genetic findings. Recent studies indicate that several major variants of PS have some characteristics of a prion disease and may therefore be transmissible. Married couples offer a unique opportunity to study person-to-person transmission and the role of shared environments as the cause of parkinsonism.

Methods: Autopsy is offered to patients seen at the Movement Disorders Clinic Saskatchewan at no cost. Five couples seen in our clinic, where each spouse had a clinical diagnosis of parkinsonism, came to autopsy.

Results: Median duration of marriage was 42 years before the Parkinson syndrome first manifested in a spouse. Three couples were pathologically or genetically discordant for Parkinson variant. Each spouse in the other two couples had Parkinson's disease. One couple had onset separated by 20 years and one partner had a strong family history of Parkinson's disease.

Conclusion: Our data indicate that neither of the Parkinson's disease, Progressive Supranuclear Palsy and Multiple System Atrophy are transmitted by sexual or other intimate contact. The data also indicate against shared environments as the cause of these disorders.

1. Introduction

Several neurodegenerative disorders of unknown etiology manifest as Parkinson syndrome (PS). The most common PS variant is the idiopathic Parkinson's disease (PD) which is characterized by marked substantia nigra neuronal loss and Lewy body (LB) inclusions [1]. There is considerable clinical overlap between different variants of PS and definite diagnosis is based on histological examination of the brain or genetic studies [2–8]. Monogenic forms of PS and PD are known in a small number of cases [6–8]. Drug induced parkinsonism is a common variant of PS which has no known brain pathology [9].

There are rare reports of conjugal parkinsonism [10–13], mostly as clinical curiosity. One study focused on shared environments as the possible cause of PS in married couples [10]. None of the studies on the conjugal PS cases to date have reported on the underlying disease process. Consequently, the concordance of the PS pathology between the spouses has not been established.

Recent reports indicate that LB pathology can spread from the host brain to healthy transplanted fetal tissue in patients with PD [14,15]. The mechanism of spread of the pathological process from PD host to the healthy transplanted tissue is a source of ongoing debate [16]. One possibility is that PD is prion like disease [16–18]. Because tissue transplant is not performed for the treatment of other common variants of PS like Multiple System Atrophy (MSA) or Progressive Supranuclear Palsy (PSP), similar information on the possible spread of pathological process to the transplanted tissue is not available in humans in these disorders. However, both the synucleinopathies [19] and tauopathies [20] have been postulated to resemble prion disorders and may therefore be transmissible.

* Corresponding author. Division of Neurology, Royal University Hospital, 103 Hospital Drive, Saskatoon, Saskatchewan S7N 0W8, Canada.
E-mail address: ali.rajput@saskatoonhealthregion.ca (A.H. Rajput).

http://dx.doi.org/10.1016/j.parkreldis.2016.07.011
1353-8020/

Animal studies show that different strains of alpha-synuclein lead to distinct types of synucleinopathy – PD or MSA [19]. Thus transmission from a patient with PD would produce PD pathology but not MSA, and transmission from a subject with MSA would lead to MSA and not PD [19,21].

Different strains of tau aggregates also produce distinct pathology which is similar to the donor, e.g. Alzheimer's disease (AD) donor transmission produces AD, corticobasal degeneration (CBD) to CBD and PSP to PSP pathology in animals [20]. Thus transmission of any of these tau pathological entities from one individual to another is expected to produce the same type of pathology in the recipients. Based on laboratory and transplanted brain studies, person-to-person transmission of PS is a possibility though it has never been conclusively demonstrated.

Sexual and other closest social contact in society is most intimate between married or otherwise cohabitating couples. Such patients offer unique opportunity to study the potential for person-to-person transmission. As a clinical diagnosis does not always predict underlying PS pathology [3–5], conclusive evidence of transmission from one spouse to the other, or shared environments resulting in PS in both spouses, can only be obtained with brain pathology studies of both spouses.

We report on five couples where each spouse had clinical diagnosis of PS, and brain pathology and genetic screening.

2. Material and methods

Movement Disorders Clinic Saskatchewan (MDCS) has been conducted by one (AHR) or two (AHR and AR) neurologists since 1968. Details have been reported previously [22]. The province of Saskatchewan has a general tax funded healthcare insurance plan which covers all residents in the province. As well, there is a universal tax supported provincial prescription drug plan. The access to MDCS is on a first come basis, except for urgent cases. Longitudinal follow-up is a major focus of the clinic [23]. In general the patients are reviewed at 6–12 month intervals [3,22–24].

First motor symptom of PS and the age at onset are recorded at first visit. Every patient is evaluated by one of the two (AHR, AR) movement disorder neurologists at each clinic visit. Up to 1987 the severity of motor symptoms of PS were evaluated by Webster Scale [25] and by Hoehn & Yahr Global Disability Scale [26]. Subsequently Unified Parkinson's Disease Rating Scale (UPDRS) has been utilized for those assessments [27]. At each assessment, the efficacy of antiparkinsonian drugs and motor complications of treatment – wearing off (WO), on-off (OO) and levodopa induced dyskinesia (LID) are assessed by the neurologist [23]. Mini Mental State Examination (MMSE) is performed in most cases at some time and in some cases serially. The diagnosis of dementia is however based on well-documented decline in cognitive function consistent with the age and education of the patient [23]. Videos are made on all consenting patients.

Patients attending MDCS are offered autopsy at no cost to the family/estate. Autopsy consent is granted by the next-of-kin after death of the patient. The body is transported to Saskatoon and autopsy is performed within 24 h of death. The autopsy consent is approved by the Saskatoon Health Region Authority and the use of brain for research is approved by the Bioethics Board of the University of Saskatchewan.

At the time of autopsy, the brain is divided at midline in two halves. One-half is immediately frozen at −80 °C while the other half is fixed in formalin and subsequently studied by neuropathologist who generates a detailed pathology report. There is no specified research protocol for pathology study. All brain areas known to produce PS are included. All commercially available stains at our institution at the time of autopsy, including alpha-synuclein, tau and ubiquitin are used for these studies. The pathology report is shared with the family of the deceased with an offer to discuss the clinical and pathological findings if the family so wishes. The final diagnosis is made by the treating neurologist considering all the clinical and pathological findings. Clinical data, videos, frozen brain tissue and where available the formalin fixed tissue remnants, paraffin blocks and slides are preserved in our laboratory [22].

History of spousal blood relationship was obtained and confirmed from the family of the study subjects for this manuscript.

Genetic screening in these couples was performed in the laboratory of MF at University of University of British Columbia, Canada. Genomic DNA was extracted from de-identified frozen brain tissue according to standard procedures. All subjects were screened for SNCA, missense mutations and copy number variants, *LRRK2* p.G2019S, VPS35 p.D620N, DNAJC13 p.N855S mutations and SCA 2, 3, 12 and 17 trinucleotide expansions as previously described [28].

3. Results

537 patients seen at the MDCS came to autopsy by the time this manuscript was prepared: 392 (73%) had a clinical diagnosis of PS and 80% of the autopsied subjects with PS had PD. Eleven couples where each spouse had clinical diagnosis of PS were seen in our clinic. In six of those either none or only one spouse came to autopsy. The remaining five couples where each spouse had a diagnosis of PS, and also came to autopsy were included in this study. None of the five couples were consanguineous. The median age of PS onset in the 10 patients was 70 (range 60–80) years. Median duration of marriage before PS first manifested in a spouse was 42 (range 32–55) years. The median duration of marriage before first death of a spouse was 58 (50–63) years. The median age at death was 84 (72–89) years. Videos were made on all 10 cases.

Table 1 is a summary of the five couples. In two couples (#3 and #4), each spouse had clinical and pathological diagnosis of PD. In couple #3 the wife had a strong family history of PD. In one couple (#1), both spouses had tauopathy but husband had clinical diagnosis of PD. He was a carrier of the *LRRK2* p.G2019S mutation [29], and has three nieces with PS who are also carriers. His pathology findings were consistent with mild PSP as well had some features suggesting corticobasal degeneration. His wife had clinical diagnosis of PSP that was confirmed at autopsy. In the remaining two couples (#2 and #5), the clinical and pathological diagnoses were discordant between spouses. In couple #2, the wife had unclassified tauopathy while the husband had PD. In couple #5, the wife had MSA and husband had PD. Table 1 shows PS onset sequence in the couples, calendar year of onset and the pathology findings. In four couples the onset was one to three years apart but in one couple (#3) the difference was 20 years.

4. Discussion

There are four possible explanations for the PS in these couples. One, transmission – sexual or close personal contact; two, shared genetics; three, shared environments and four, incidental PS.

We may assume that the spouse manifesting PS first transmitted the same to the other spouse. Parkinson's disease, MSA and PSP each has been postulated to have some prion-like characteristics [16–21]. Iatrogenically transmission of Creutzfeldt-Jakob disease (CJD) is well known but there is no report of conjugal CJD. In one CJD like reported couple, prion protein was not detected in either brain on subsequent studies of the brains [30]. A large study of familial CJD from Finland found no conjugal cases of CJD [31,32]. To our knowledge there is no reported conjugal transmission of a prion disease.