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Are genetic and sporadic Parkinson's disease patients equally susceptible to develop dementia?

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ABSTRACT

The occurrence of dementia in genetic Parkinson's disease is heterogeneous. The onset and progression of diverse forms of familial Parkinson's disease might be different than that of sporadic disease. Since dementia is an age related process, its risk increases with advanced disease severity and duration. The onset and progression of dementia is expected to vary between genetic forms, which present at diverse ages with different symptomatologies. It seems that genetic Parkinson's disease variants in which Lewy bodies are the prominent pathological hallmark — such as in PARK1, PARK4 and PARK8 — dementia is part of the phenotype. On the contrary, in PARK2 which is not accompanied by Lewy body accumulation, patients do not show a systematic cognitive decline. This review presents information on dementia in genetic forms of Parkinson's disease.

1. Introduction

The fact that Parkinson's disease (PD) is accompanied by the development of dementia is nowadays well accepted. PD dementia (PDD) is a cognitive and neuropsychiatric disorder that occurs in PD patients [1]. As such, it is a prerequisite that the patient's core of diagnosis is PD and PDD diagnosis follows at least one year after PD onset with cognitive decline [1]. The occurrence of PDD in genetic forms of PD is heterogeneous. The onset and progression of diverse forms of familial PD might be different than that of sporadic disease. Since PDD is an age related process, its risk increases with advanced disease severity and duration [1]. The onset and progression of PDD is expected to vary between diverse genetic forms, which present at different ages with different symptomatologies.

A long standing debate has been focusing on the issue whether PDD is in fact PD with co-existent Alzheimer's disease (AD) pathology [2]. While AD affects about 10% of the population above the age of 75 years [3], PDD is as common as 80% in this age group [4]. In this context, it is possible that PDD has been more linked to Lewy body pathology than co-existent AD related tau pathology. Some insight to the contribution of Lewy body pathology might come from observations in the domain of the genetic forms of PD.

Cognitive decline does not follow the same course in sporadic and familial PD patients. A study of the age at onset and progression of PD, with (FH) and without (NFH) family history, in 240 PD patients [5], found that the age of PD onset was younger in patients with a family history of PD, and, the duration of PD until dementia was about 10 years for FH versus 5 years for NFH. Mental deterioration, however, showed a less steep course in familial PD patients.

Nowadays, since several genetic forms of PD have been described, it would be too simplistic to compile together the course of cognitive decline in all known genetic forms of PD. This review presents information on PDD in genetic forms of PD.

2. PARK1 and dementia

PARK1 (MIM 168601) is a rare form of autosomal dominant PD [6]. The affected gene encodes α-synuclein (SNCA), which is the major component of Lewy bodies associated with PD [7]. SNCA was found associated with brainstem-type and cortical Lewy bodies in PD and Lewy body dementia, (LBD) [8]. Aggregated SNCA proteins form brain lesions that are hallmarks of neurodegenerative synucleinopathies, and oxidative stress are implicated in the pathogenesis of some of these disorders. Antibodies to specific nitrated tyrosine residues in SNCA, demonstrate extensive and widespread accumulation of nitrated SNCA in the signature inclusions of PD, LBD, and multiple system atrophy, (MSA) [9]. The predominant form of SNCA within Lewy bodies, isolated from brains of patients with LBD, MSA, and PARK1, was phosphorylated at ser129 [10]. Other biochemical characteristics of SNCA in Lewy bodies included ubiquitination and the presence of several C-terminally truncated α-synuclein species. The pathology of PDD includes three types of major changes. These include the subcortical pathology with the degeneration of the substantia nigra pars compacta, the presence of tau pathology and Lewy bodies [1]. Apaydin et al [11] found Lewy bodies in 92% of demented patients. The burden of diffuse or transitional neocortical

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and limbic Lewy bodies was 10 fold in demented versus non-demented patients. They found a modest correlation between cortical Lewy bodies and senile plaque count. In another study, the presence of Lewy bodies predicted best the presence of dementia [12]. The close relationship between cortical Lewy body burden and PDD would implicate that dementia could be a common feature in genetic forms of PD that show Lewy body pathology, such as PARK1. In this context, Nishioka et al identified heterozygosity for duplication of the SNCA gene in 2 of 113 Japanese probands with autosomal dominant PD [13]. In the first family, 2 patients with the duplication had typical PD, whereas 4 duplication carriers, over the age of 43 were unaffected, yielding a penetrance of 33%. In the second family, one affected and two asymptomatic members had the duplication. The affected patient from the second family developed dementia 14 years after diagnosis of PD. *SNCA* duplications are not confined to PARK1 patients and might also occur among sporadic patients. Ahn et al. identified *SNCA* gene duplication in 3 of 906 Korean PD patients [14]. Only one patient had a family history of the disorder; he presented early onset at age 40 and rapidly progressive disease complicated by dementia. Two of his brothers with the duplication were asymptomatic at 51 and 47 years, respectively, indicating reduced penetrance.

SNCA multiplication might show a gene dosage effect concerning dementia. Fuchs et al. reported a Swedish family with parkinsonism due to duplication of the SNCA gene [15]. The proband presented with dysautonomia, followed by rapidly progressing parkinsonism. Family history revealed multiple affected members with a similar disorder. Features of dementia, including hallucinations, occurred late in the course of the disease. Beyer et al. demonstrated an overexpression of SNCA112 in the brains of patients with Lewy body dementia [16]. SCNA98 expression was increased in the brains of patients with LBD, PD and AD, compared to controls. The authors postulated that differentially spliced SCNA isoforms may have different aggregation properties, which may be important in the development of neurodegeneration and cognitive decline as its consequence.

Spellman described a family in which multiple members in 4 generations had autosomal dominant parkinsonism, beginning in their thirties and progressing rapidly to death in 2 to 12 years. This extended family was of English and German origin and was later referred to as the 'Iowa kindred' [18]. The proposita developed parkinsonism at age 45 and died 6 years later. She had typical features of PD, except for an absence of rest tremor, although this was present in the other affected family members. Neuropathologic examination confirmed the diagnosis of Lewy body parkinsonism. The disorder was characterized by early onset, early weight loss, and rapidly progressive dopa-responsive parkinsonism, followed by dementia, and, in some, by hypotension. Intellectual dysfunction began with subjective memory loss and objective visuospatial dysfunction, and was followed by decline of frontal lobe cognitive and memory functions. Neuropathologic examination of autopsied cases showed neuronal loss in substantial nigra and locus coeruleus, as well as widespread Lewy bodies, many of them in the cerebral cortex; those in the hypothalamus and locus ceruleus were often of bizarre shapes. Other findings were vacuolation of the temporal cortex, unusual neuronal loss, gliosis in the hippocampus (CA 2/3), and, neuronal loss in the nucleus basalis of Meynert. There were no neuritic plaques, neurofibrillary tangles or amyloid deposits. Positron emission tomography in 3 patients showed decreased striatal uptake of fluorodopa. Neurochemical analysis of an autopsied brain showed a pronounced decrease in choline acetyltransferase activity in the frontal and temporal cortices and hippocampus, and, a severe depletion of striatal dopamine with a pattern not typical of classic PD. Gwinn-Hardy et al. reported neuropathology findings of the proband from the Iowa kindred [17]. There was striking cortical pathology, with regions of spongiosis and gliosis that were also rich in many thread-like dystrophic cell processes. These were accompanied by scattered glial cells with SNCA-immunoreactive inclusions, somewhat similar to glial cytoplasmic inclusions of MSA. There were also glial inclusions in the cerebral and cerebellar white matter and in certain white matter fiber tracts, in the basal ganglia and basal forebrain. The number and distribution of cortical Lewy bodies were consistent with neocortical stage of LBD. Farrer et al. described a family of Swedish American descent with autosomal dominant early-onset parkinsonism and dementia due to a triplication of the *SNCA* gene [18]. The proband, which had onset at age 31, had rapidly progressive parkinsonism with tremor, rigidity, and bradykinesia. At age 45, he developed visual and auditory hallucinations and paranoia. He later developed intellectual impairment, progressing to severe dementia with mutism, followed by death at age 52. Postmortem examination showed severe neuronal degeneration and loss in the substantia nigra, locus ceruleus, and hippocampal areas CA 2/3. Lewy bodies were present in the hypothalamus, basal nucleus of Meynert and the cerebral cortex. The latter is an unusual feature for PD, although Lewy neuritic pathology is often abundant in LBD [19]. None of the patients developed the atypical features reported in diffuse Lewy body disease, such as hallucinations, or behavioral disturbances. No other affected individuals from these families were available for molecular studies, but both mothers were affected and, according to the family history, they also presented with typical parkinsonism and survived until the age of 80. These findings are in contrast with those for *SNCA* triplications, for which the mean age at onset was earlier (38 years, SD 9) for patients in whom it was precisely determined and disease progression was severe, associated with dementia and hallucinations. These data strongly suggest that the severity of motor and cognitive features might be influenced by SNCA burden.

A recent study showed that not only *SNCA* triplication but also *SNCA* duplication could induce severe dementia [20]. Thus, multiple copies of the *SNCA–MMRN1* region are an important cause of parkinsonism with dementia [20].

3. PARK2 and dementia

Mutations in *parkin* gene, located at 6q25.2–6q27 (PARK2, MIM 602544), are the most common cause of inherited PD, accounting for up to almost half of familial recessive early-onset PD cases [21,22]. This autosomal recessive young-onset PD is symptomatically different in several aspects from classic late-onset PD, although classic symptoms of PD, such as bradykinesia, rigidity and tremor, are present [23–25]. Hayashi et al. reported neuropathology findings in a Japanese patient with a mutation in the PARK2 gene [27]. Loss of neurons and gliosis were most pronounced in the medial and ventrolateral regions of the substantia nigra pars compacta and in the locus ceruleus. Remaining neurons had low amounts of melanin. There was mild neuronal loss and gliosis in the substantia nigra pars reticulata. No Lewy bodies were identified. Some neurofibrillary tangles and senile plaques were observed in the cerebral cortex, although there was no clinical evidence of dementia. Another study also found no Lewy bodies, but diffuse tau pathology [26].

Despite the fact that *parkin* patients do not usually develop dementia, they might show increased susceptibility to psychiatric disturbances. Heterozygous *parkin*, as well as *PINK1* mutation carriers, often develop neuropsychiatric disturbances [28–30]. Susceptibility to psychiatric illnesses was also reported in asymptomatic *parkin* mutation carriers. Khan et al found 17 % of psychiatric disturbances in relatives of 16 unrelated *parkin* disease patients [31]. In this context, it is of interest that a locus for schizophrenia has been mapped to chromosome 6q25, adjacent to PARK2 [32].

4. PARK6 and dementia

In a review of 21 patients with *PINK1*-related parkinsonism (MIM 605909), reported in the literature, Albanese et al. found that most of the patients had slow disease progression, good response to levodopa,