

Dementia in Parkinson's Disease Revisited: In the Light of Fischer's Disease

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Abstract

This article discusses in the main two topics through literature review: (1) Patients with Parkinson's disease (PD) either have been said on the one hand NOT to result in dementia, or (2) they may on the other hand result in dementia. The purpose is motivated by my intention to look into the reason why, after James Parkinson's "insight" in 1817, he explicitly excluded intellectual deterioration from the disease, and whether later researchers have followed the wrong path or not. The latter is then claimed to be Parkinson's disease Plus which is often said to come from a concomitant of DAT (dementia of Alzheimer type), thereby upholding the former.

Such being the case, I contend from two angles below, over and above the usual description of movement disorders which fall outside the domain of my purpose. Notwithstanding, however, I stress that such movement disorders ensue from none other than wear and tear in the brain functions of PD patients, and therefore inevitably lead to dementia for sure. Thus, besides my two contentions below, I shall conclude by extension that patients with PD are bound to have apoptosis which ensues on dementia besides having movement disorders. The two angles of my contention are as follows:

1. Since gradual apoptosis (cell death) occurs in the brain of patients with PD – or in the brain of any other patients with a neurological disorder -- on account of the malfunctions of dopaminergic neurons or substantia nigra in the subcortical structures, affecting the brain functions of memory and cognition, PD patients are bound to result in dementia; the affected brain functions of memory and cognition owe to wear and tear accelerated by PD itself, contrary to the claim by most experts, because such affected brain functions of memory and cognition are the source/cause of dementia, whether they like it or not.
2. Such dementia is not at all due to DAT as a concomitant of wear and tear, because AD is a fiction, but most likely to PD itself, beside two other causes: (1) Lewis Bodies and/or (2) Fischer's presbyophrenia in Fischer's disease both of which are wear and tear of non-vascular origin in the case of PD, but of glandular necroses as its substrate in the case of Fischer's Disease (FD).

Keywords: *Dementia; Parkinson's Disease; Fischer's Disease*

Introduction

In the medical literature, several assertions can be ascertained, which have been made by investigators of dementia in Parkinson's disease (PD) since 1817 with hundreds of publications but without success. They represent ideas and views, in response to the urge of research interest and/or necessity for clinical purposes, to deal with the conflicting reports of prevalence from 20% to 81% in the literature. Such urge and research interest have resulted in two claims: (1) that patients of orthodox PD do not result in dementia; (2) but that if they are found to result in dementia, the disease is then claimed to be Parkinson-disease plus. Because of the insistence to uphold the first claim – PD does not result in dementia -- the second claim is now modified as Atypical Parkinsonian Disorders, Litvan [1].

There is no doubt that the intention of each assertion was to solve or ascertain the long-standing problem of whether or not dementia can occur in patients with PD; the aim has been to clarify Parkinson's "intuition" that there was something peculiar about the mental state of Parkinsonian patients. However, the solution is still not within reach; in fact, the experts on PD introduced more questions for the problem than the answers they had intended to provide, ignoring the pivotal issue of apoptosis that is bound to occur in any brain disease, PD or otherwise. Hence, there is a need to revisit the problem, from the perspective of dementia presented in my "Senile Dementia and Oskar Fischer's Presbyophrenia: The Forgotten Giant's Contributions", Peng [2] in the hope that this time the problem can be clarified, if not solved, on the basis of the neurobehavioral approach outlined in Peng [3] in which, as the first article in a series of three, I conclude that AD is a fiction.

After the said article published in *EC Neurology* [2] as the second one, this article as the third one in the series is intended to revisit dementia in Parkinson's Disease (PD), not from the point of view of AD, as it is a fiction, but in the light of Fischer's Disease (FD), by replacing AD with FD. In so doing, I will somewhat elaborate Fischer's dichotomy of Simple Dementia and Presbyophrenic Dementia to also touch on dementia with Lewis Bodies (DLB) in the discussion for a comparison.

Such ideas and views in the current literature on PD may be roughly divided into four assertions as follows: First Assertion: Dementia does occur with PD as a part of the clinical picture of PD, and increases severity as PD worsens. Second Assertion: Dementia does occur in PD but it differs from dementia of the Alzheimer type (DAT, whatever that is). Third Assertion: There are patients with PD who are demented and there are also patients with PD who are not demented, thereby proposing two different paradigms of PD; by calling the former Parkinson Disease Plus because of alleged co-morbidity with DAT; Fourth Assertion: There are experts who insist that true dementia (whatever that is) is difficult to diagnose, because it is equated with AD or considered a disease when it is not, without knowing that AD is a fiction, never existed, does not exist, and will never exist, especially so when it is said to occur in PD; therefore, they recommend that possible treatable causes for the dementia must be excluded first before a definitive prevalence can be determined for PD.

In spite of the diversities, there are also similarities in all assertions:

1. Dementia in PD or AD – even though AD never existed as it is a fiction, Peng [3]--- or any other degenerative brain disorder that results in dementia is considered an add-on disease as a given without defining what dementia is, because dementia is not a disease.
2. All investigators of the assertions regard memory impairment in relation to intellectual decline as a yardstick to measure the presence of dementia.
3. The investigators of such ideas and views tacitly employed language in the brain as a convenient "tool" in their assessment of dementia, e.g., orientation, recall of recent and past events, retention of digits and names of common subjects, calculation, general information, and judgment.
4. But none of them openly recognize degenerative language disorders as the main criteria for the evaluation of dementia in PD, because they do not know what language in the brain is. They even presume that everybody knows what language is or believe that it is lateralized to one hemisphere, when language in the brain is behavior which is memory-governed, meaning-centered, and multifaceted on the ground that sign language is now considered a language in its true sense. For such a formidable reason, I stress that language in the brain can never be lateralized to one hemisphere or localized at all [4].

In view of these similarities, I should add that all behaviors, language behavior in particular, use varying body parts to make proper adjustments to the internal and external environments. It is the distinction of proper or not in the production of behaviors by PD patients or other patients, as viewed by the receiver of such behaviors, e.g., a physician or a family member, that determines the presence or absence of dementia, as well as the degrees of dementia or any neurological disorders, if dementia is determined to be present.

Even if language disorders are taken into account, all neuropsychologists dealing with the subject tend to separate language and speech, for instance, Frattali and Duffy [5], without giving much thought to the fact that speech is a part of language. This view in neuropsychology, when dealing with dementia, is further complicated because sign language is a language in its true sense and yet there is no speech in sign language. Unless the separation of language and speech is abandoned, because speech is a part of language, and the whole notion of language in neuropsychology as well as in aphasiology is drastically changed or at least modified to include sign language, problems will arise; deaf people who are native signers are not immune to PD or dementia nor to any other degenerative brain disorders.

I have thus sensed that a fundamental element is missing in those assertions, which is crucial to the quest of whether PD patients will have dementia or not during the entire course of their illness. For this reason, I decide to devote this article in association with Peng [2] and Peng [4] in order to help solve the problem, by considering to some extent Fischer's disease, as AD is now a fiction [3], as well as Fischer's dichotomy of simple dementia and presbyophrenic dementia in PD.

Because of the differences in and similarities among those ideas and views in the literature, I shall therefore devote a brief review of each of those assertions first. I will then, as a reflection, allude to the literature review of the historical development regarding the concept of dementia already presented in [2] to some detail, which is the core of solving the whole problem of DAT, dating back to the nineteenth century. In so doing, it is hoped that a clearer and better understanding of what dementia in PD really is can be ascertained. The reason is straightforward: dementia is bound to ensue from each of such degenerative brain diseases as FD, PiD, MS, SCA, and the like, PD being one of them, as well as from medical condition like Epilepsy, because apoptosis occurs in each one of them. It is then hoped that the quest of dementia in PD can be accomplished and understood once and for all.

After the literature review, my ideas and views from a different but new perspective will be presented in order to prove that every patient diagnosed to have PD will develop dementia over time, be it called senile dementia or not. This new perspective is that if any neurological disorder involves apoptosis, dementia is bound to ensue as a consequence to end up in FD as Fischer's presbyophrenia before expiration. I will also cite a vivid example from an article published in *EC Neurology* regarding a case of the misdiagnosis of AD, termed Atypical AD, in a patient who was claimed by her daughter to have died of it for a comparison.

Finally, this article will conclude that (senile or presenile) dementia is a continuum of the degenerative brain functions of memory, owing to wear and tear, and therefore is not a disease; rather, it is the differential manifestation of behavioral alterations due to deteriorating brain functions of memory. Therefore, its clinical manifestation varies from one patient to another. This view of dementia is hereby taken as my point of departure.

Literature Review on the Assertions of Dementia in PD

In the present context, dementia is not considered a disease, any more than it can be equated with AD, because AD is a fiction [3]. The reason why dementia had been excluded in the literature of movement disorders – owing presumably to Parkinson's "intuition" in 1817 -- was due precisely to this very erroneous notion of dementia being a disease or equivalent to AD. Thus, if a PD patient developed dementia, it was considered an "add-on disease", thereby leading to the once popular idea of "Parkinson's Disease-Plus Syndrome" as if there was a co-morbidity of two degenerative diseases. However, since the "Parkinson's Disease-Plus Syndrome" is now considered obsolete, switching to a new concept known as Atypical Parkinsonian Disorders, Litvan [1] which is equally problematic, the probability of PD patients having dementia has become rather obvious.

It is in the context of this new development regarding the neurodegenerative nature of PD that I shall review the literature, along the four assertions listed above: (1) to see why dementia had been excluded in the consideration, diagnosis, and treatment of PD – owing most likely to Parkinson's exclusion in 1817; (2) to also point out that, if it has not dawned on movement disorders experts already, dementia is a de facto part of the course in the deterioration of PD, and will ensue sooner or later, once a patient is diagnosed to have it; and at the

same time, (3) to state that the co-morbidity of dementia in PD is NOT at all AD –because it is a fiction and dementia is not a disease– but rather it is due to the fact that PD causes apoptosis, and therefore such a dementia in PD could very well be diagnosed as the result of the co-morbidity of Fischer's disease (FD).

Review of The First Assertion

The investigators of this assertion suggest that there was an evident association between the stage of the disease and the frequency of dementia. This finding indicates that the subcortical structures are thought to play a significant role in the pathophysiology of dementia in PD, because of apoptosis, even though these investigators do not acknowledge it. Such a finding is well taken, however, provided that apoptosis in PD is also taken seriously in the present context, apparently not by those investigators, or else there would not be any movement disorders.

The thrust of this assertion hinges on the prevalence of dementia in patients with PD. But because there seems to be no common ground for the definition in the understanding of what dementia is, the findings in the literature of this prevalence of dementia in PD vary from 20 to 81 percent: Pollock and Hornabrook [6]; Celesia and Wanamaker [7]; Markham, Treciokas, and Diamond [8].

Among these investigators, even though there is no overt understanding of what dementia is, there are also disagreements of the criteria for establishing the occurrence of dementia. On the other hand, there are also other suggestions that the dementia in PD was due to concomitant DAT (dementia of Alzheimer-type) for two reasons:

1. Identification of DAT histopathologically changes in the brains of some patients with PD.
2. The atrophy of the nucleus basalis of Meynert, the source of cholinergic innervation of the cerebral cortex, varies, because both PD patients and DAT patients are said to have it.

Given these two reasons, one point deserves comment here for this assertion. The investigators regard dementia in PD and DAT as the same disease without defining what dementia is to cultivate a common ground for understanding. In other words, they take dementia in PD as the consequence of Alzheimer-type due to histopathologic changes and/or atrophy of the nucleus basalis of Meynert, implying of course that cell death (apoptosis) is the cause of dementia in PD and of DAT, but that such cell deaths may occur in the cerebral cortex (in the case of DAT) or in any of the subcortical structures (in the case of PD). However, the point I want to emphasize is that what if and when AD is now proven to be a fiction, cell death remains prevalent in all neurological disorders, including epilepsy (TLE or extra-TLE among others), to ensue in dementia as a neurological disorder. I have prepared another manuscript, entitled "Dementia in Epilepsy: A Clinical Contribution to the Metabesity of Epileptology, Geriatrics and Gerontology", for publication to address such an issue and define what the contribution should be.

In that article, I shall point out, however, that the connections with geriatrics and gerontology are limited to Epileptology dealing with adult epilepsy. The reason is that padoepilepsy (children's epilepsy) due for instance to cortical dysplasia, single or multiple, hinges on the pediatric epileptic patient's development for schooling and the acquisition of a language, whereas adult epilepsy involves aging, rather than growth. Therefore, there is no connection of Epileptology regarding children with Geriatrics and Gerontology.

The exclusion is based on my theoretical construct of changes in life from birth, growth, maturation, to old age. Growth: after birth to the age of 18. Maturation: from age of 18 to 35, after which neurons start to disappear. Old Age: after age 35 to death, because statistics shows that from 35 to 80, apoptosis, not limited to neuronal losses, increases the speed gradually to reach some 20% or more at autopsy. This theoretical construct forms the base of wear and tear for aging. More will be described regarding the details in this third article of the series mentioned above.

I must hasten to remind the reader, however, that Alzheimer's single patient, Auguste, had four brain diseases [3]. not two hallmarks which seem to have been taken as a given in this first assertion, and that this patient's brain was evenly atrophic, not limited to atrophy of the nucleus basalis of Meynert, besides her internal and external hydrocephalus. Thus, what is DAT seems not at all clear, because AD never existed, does not exist, and will never exist, despite the popular assertion to the contrary in the medical fields. Does it refer to the behavioral alterations as briefly described in Alzheimer's 1907 paper or to the organic diseases, like the "two hallmarks", inappropriately or erroneously alluded to by Alzheimer in 1911?

Recall that Alzheimer in 1907 spent only two sentences to mention senile plaques, a couple of short paragraphs to describe neurofibrillary tangles of which he was not at all sure of the pathogenesis; moreover, he never described or could not describe the behavioral alterations due to the arteriosclerosis and/or the evenly atrophic brain (nor could anybody else, except Fischer, do so at that time), not to mention that he spent only one sentence or so to touch on the involvement of glial cells in his second patient, by attributing plaques in 1911 to Fischer's plaques. Thus, the attempt in the past to link DAT to dementia in PD can only be a farce, at best a failure, because DAT has never been described clinically, pathophysiologically, or otherwise in a clear manner, as if everybody seemed to know what it was; therefore, I assume that it was taken for granted, probably or tacitly referring to the "two hallmarks".

The question I want to raise then is this: Since Alzheimer in 1906 did NOT discover a "new disease" which Bonfiglio and Alzheimer himself found "difficult" to fit into Kraepelin's then ruling paradigm of dementia praecox or senium praecox for a nosological classification, how can there be DAT in any PD patient?

Review of The Second Assertion

Unlike the previous one, the investigators in this assertion, Cummings, Darkins, Mendez., *et al.* [9], are more overt in their attempt to compare dementia in PD and DAT. In so doing, they have inevitably tried to dissociate dementia in PD from DAT, using language and speech as the main criteria. But here is a significant finding in this assertion. That is, dementia in PD is a subcortical dementia which is similar to that in progressive supranuclear palsy (PSP) and Huntington's disease (HD) for reasons of the dysfunction of basal ganglia and frontal-subcortical connections, Cummings, Darkins, Mendez., *et al.* [9]; Albert, Feldman, and Willis [10].

Because of such findings, three comments may be worthy of mention here:

1. Investigators in this assertion, like Cummings., *et al.* [9], divide their PD patients into PD without overt dementia and PD patients with overt dementia.
2. They make a distinction between language and speech in their testing.
3. As a result, they conclude that the profile of language abnormalities in PD and that of DAT differ in terms of the relationship between dementia severity and speech and language changes.

The first comment is that the superficial division of PD patients with and without overt dementia implies or presupposes that those patients without overt dementia will eventually become overtly demented as their PD worsens later because of its neurodegenerative nature. Thus, there was no need for them to exclude other causes of parkinsonism from idiopathic PD, e.g., postencephalitis, arteriosclerosis, and the like.

Such a decision is only partially correct for the following reason: Whatever the cause of parkinsonism, it is the continuing cell death (apoptosis) that first affects the dopaminergic neurons in the substantia nigra; it then triggers the dysfunction of the cholinergic innervation in the basal ganglia to result in the initial symptoms of dementia which will worsen as the cell death continues. Put differently, Lewy bodies in idiopathic PD, postencephalitis, arteriosclerosis, or the like do not cause dementia; rather, each of these diseases causes apoptosis of the brain which then infringes on the brain functions of memory to result in dementia of the patient.

As to the second comment, it may be stated that the distinction between language and speech in their test battery is uncalled for. Their desire to distinguish dementia in PD from DAT on the basis of language and speech characteristics may have been well intended. But the results presented are misleading. The reason is that speech is a part of language which has two planes; namely, content plane and expression plane [4,11]. Only when the two planes are put together, through catalytic mapping, is there language in the brain. More is discussed extensively in [4] about content plane and expression plane and their relationships in terms of catalytic mapping for speaker's construction of meanings and coupling for hearer's reconstruction of meaning. That is, the meaning hearer reconstructs is nine times out of ten not the same as the meaning speaker constructs.

From the neurolinguistic point of view for the third comment, then, the investigators assume that both PD patients and DAT patients have language disorders; I am of the opinion that they think PD patients have worse language disorders in their expression plane while DAT patients have worse language disorders in their content plane, even though I am sure these investigators do not have any clue of what these two planes are or what language in the brain is like. Nevertheless, the bottom line is that any damage to the nervous system, cortical or subcortical, caused by vascular or non-vascular factor (e.g. by a scalpel), will result in dementia, albeit gradually, because of apoptosis. Thus, only patients of PD, whatever type, are bound to ensue in dementia gradually owing to the ongoing process of wear and tear [3]; there is no such thing as DAT (whatever that is), albeit the symptoms of some kind of neurological disorders, not at all DAT, may occur later as a co-morbidity in the course of wear and tear to further complicate dementia for sure.

Although initially the dementia of PD patients may look different from that of patients with a neurological disorder apart from PD at least ostensibly, as each of these neurological disorders progresses, their language disorders and the resulting dementias will eventually be indistinguishable, because the final stage of neurological disorders in PD patients, as manifested in the brain dysfunctions of memory and cognition, and that of the non-PD patients are indistinguishable, if not the same, unless laborious efforts are taken longitudinally to differentiate the disordered language behaviors in terms of phenomenology. Put differently, both PD patients and non-PD patients become mute and bed-ridden, with or without hallucination in varying forms, visual or auditory, and will be equally demented in both the content plane and the expression plane; that is, with severe language disorders.

In terms of the content plane and the expression plane, put differently, PD patients without overt dementia also have language disorders which, as the severity of their PD worsens, will show up as dementia later. In other words, these patients will become patients with overt dementia. The problem or the task remaining is therefore threefold: (1) to map out the course of degeneration from PD patients without overt dementia to PD patients with overt dementia; (2) to ascertain whether such a course of degeneration in PD resembles that of non-PD neurological disorder throughout the final stage; and (3) to determine the pathogenesis, if there are resemblances, in terms of behavioral alterations or, if not, what the differences may be.

Review of The Third Assertion

This assertion may be regarded as a corollary of the second assertion I just commented on above; the investigators Lieberman A, Dziatolowski M, Kupersmith M., *et al.* [12] go one step further to claim that PD with dementia (i.e., with overt dementia) may represent a different disorder from PD without dementia (i.e., without overt dementia). In line with such an observation, then, it is interesting to note that these investigators originally thought that dementia was not a part of PD but represented the chance occurrence of PD and AD in the same patient, Lieberman A [13].

However, in this assertion, the investigators now believe that the dementia is more likely to be related to PD than to aging [12]; in keeping with their assertion, they have added that features indistinguishable from those of AD, including neuron loss, senile plaques, and neurofibrillary tangles in the neocortex, are more commonly found at autopsy in PD than in the brains of age-matched controls, Alvord EC, Forno LS, and Kusske JA [14]; Brown RG and Marsden CD [15]; Hakim AM, and Mathieson G [16].

It therefore follows that four comments deserve some mention here: The first comment is that the investigators first believed that dementia was not a part of PD but later changed their mind to believe that dementia is more likely to be related to PD, a change that is a 180 degree about-face. Such a drastic change is common in the academic world. However, it implies that dementia in PD to them is a disease which is the same disease as DAT (without knowing that AD is now a fiction); the implication is that their view is shared by many neurologists. On the other hand, it also implies that if dementia is not a disease but it happens in PD patients, then a different interpretation of dementia in PD must be called for. The only plausible interpretation is that PD causes apoptosis which consequently ensues as dementia in the patient because of wear and tear which is due to PD itself, unless something else is involved, which is likely to be either Lewy Bodies or Fischer's Presbyophrenia in FD.

The second comment is that they seem to suggest that the disease includes neuron loss, senile plaques, and neurofibrillary tangles which are the causes of dementia in both PD and AD (without of course knowing that AD is a fiction). In this regard, then, there is no distinction between the first assertion of dementia as a part of the clinical picture of PD and this view of the third assertion.

The third comment is that as they base their assertion on the age of onset, with the age of 60 years as the dividing line between demented PD patients (12% below 60 years) and non-demented patients (24% below 60 years), they draw a rather interesting conclusion. They believe they can distinguish two separate disorders of PD: "one, an exclusively motor disorder occurring in a younger population with a longer and more 'benign' course and a better response to levodopa; and, the other, a motor disorder followed by a cognitive disorder occurring in an older population with a course of more fulmination and a poorer response to levodopa", Lieberman A, Dziatolowski M, Kupersmith M., *et al.* [12]. It is this view that led the investigators to challenge the first assertion held by Marttila and Rinne [17].

The fourth comment is that this third assertion goes counter to the second assertion which takes into consideration, on anatomical and linguistic ground, subcortical dementia in PD versus cortical dementia in AD. But now that AD is a fiction, where would this third assertion go? I presume that Fischer's presbyophrenia is the only outcome of PD patients at the end, as will be shown in a vivid case of misdiagnosed AD quoted further below.

Review of The Fourth Assertion

This assertion takes a skeptical view in that the investigators want to exclude dementia from PD which, to them, means idiopathic (i.e., true) PD. But even a more conservative estimate of prevalence has also one in five patients with PD demented; therefore, the idea of exclusion becomes suspect. Their rationale is that it is difficult to assess and diagnose dementia in PD, because many of the problems are compounded by other aspects of the disease, e.g., Brown RG and Marsden CD [15].

It is of interest to note that they think that the difficulties are reflected by the conclusion of Benton and Sivan and others, as in (1) Benton AL and Sivan AB [18], saying that "dementia is simply a nonspecific diagnosis of behavioral incompetence referable to brain disease", and (2) Brown RG and Marsden CD [15]. This conclusion is just as nonspecific, to say the least, even though Brown and Marsden believe that "the severity of the impairment is difficult to define objectively", Brown and Marsden [15].

As a possible way out, they mention the notion of occupational and social incompetence emphasized in DSM-III [19] (1980). They then refer to the idea that "In Alzheimer's disease, the commonest dementia, memory impairment, usually precedes changes in mood and behavior, e.g. Sim M, Turner E, and Smith WT, [20], whereas in other dementias, such as Pick's disease or HD, it may be preceded by disturbances in mood, personality, and behavior, Lishman WA [21].

The investigators go on to say five things:

1. The need to discriminate between progressive dementia and temporary impairment related to confusion or depression by the use of MSE (mental state examination) in combination with interview.

2. A complaint that while a combination of interview and MSE is probably the most reliable method of assessment used, the range of prevalence estimates so obtained is still wide, varying from 20%, Lewy FH [22], to 81%, Martin WE, Loewenson RB, Resch JA, and Baker AB [23].
3. Their insistence that important sources of such variation in these studies lie elsewhere.
4. A recommendation that such estimates must be interpreted in the context of the prevalence of dementia in the general population (5% severely demented and 5% mildly demented for those over 65 years of age).
5. A suggestion to think in terms of additional risk for PD patients, above and beyond the expected for the normal population, thereby arriving at the range of 10 - 15% dementia in PD, Brown RG and Marsden CD [15].

Two comments on their skepticism require mention here: (1) Their skepticism will disappear once the notion of dementia is clarified and better understood; the reason is that, like all the other assertions, it seems that they regard dementia as an add-on disease when it is not. (2) All diseases are additional risks to the process of "normal aging" the causes of which remain to be grappled with by gerontologists; PD is no exception, especially when it is a neurodegenerative disease, idiopathic or otherwise, because one of the costs of such a disease the patient has to pay is dementia.

The important point here is that "normal aging" is a relative concept. It means that the majority of people undergo the same fate, and therefore nobody can complain about the final destination of the fate which is death. But when a disease occurs, whatever it may be, within a selected group, it speeds up the path the process of "normal aging" --- wear and tear --- treads on for that group.

Of course, traffic accidents, food poisoning, and the like can also cut short the process of "normal aging" to reach the final destination. If the investigators' skepticism is insisted upon, they will reach a theological conclusion of "predestination": those who are bound for a short-cut, including suicide, versus those who take the full course of "normal aging" if that is really possible. Even if it is possible, the task of predicting statistically the prevalence of how many such people can do so will be an unthinkably formidable one.

Brief Literature Review on Dementia as an Aphasia

Since the beginning of the notion of senile dementia was arbitrarily taken to have begun from 1892, I should now describe the connection between (senile) dementia and aphasia. However, caution must be exercised again that there were other neurological causes which got into the picture in the contest between Fischer and Alzheimer regarding who had the proof of the organic cause of senile dementia. Recall that Fischer proposed presbyophrenia as the anatomical-neurophysiological substrate of senile dementia but Alzheimer simply avoided the issue by postponing his conclusion (decision). One such neurological cause was, of course, Pick's disease [24].

In that important article, which marked the beginning of Pick's disease, he described the disease affecting the left temporal lobe predominantly and characterized by aphasia, thereby setting off a new paradigm. Take note that the disease was affected NOT by Broca's area in the left frontal lobe but by the left temporal lobe, sparing the so-called Wernicke's area. Therefore, Pick's disease was to be continued in a rather different way in that it became the "traditional image" of Pick's disease that emerged later, which is that of a dementia characterized by signs of frontal lobe dysfunctions Graff-Radford NR, Damasio AR, Hyman BT, *et al.* [25] and Kertesz A [26]. The point I wish to make is that the so-called traditional image as cited above differs drastically and deviates from Pick's original description of the lesion site.

Be that as it may, before Pick's publication, Paul Broca's publication in 1861 and Wernicke's publication in 1874 had already appeared. Therefore, Pick was aware of such publications. That is, aphasia in the sense illustrated above (i.e., language disorders) caused by any degenerative brain disease had been known before Pick's original description in 1892, As a result of his awareness, he called the symptoms of his case "amnestic aphasia" (aphasia due to forgetfulness), without implicating Broca's or Wernicke's area. It then led to subsequent semantic confusions in three ways:

1. Aphasiologists qua neurologists misidentify Pick's disease, AD, and any other form of dementia as aphasia;
2. Experts on dementia began to use aphasia as a criterion to diagnose patients with dementia as AD; and
3. Experts on movement disorders began to separate unwittingly language and speech, as was pointed out above, to distinguish two kinds of PD when PD patients all have language disorders, which include speech disturbances, without realizing that speech is a part of language.

The problem here is contest for "territoriality" in the nosology of diseases when neither dementia nor aphasia is a disease; in other words, experts on AD want to claim aphasia as a part of AD and aphasiologists qua neurologists want to claim dementia of any kind, AD and Pick's disease in particular, as aphasia which is also a disease to them, Kertesz [26], forgetting that Pick's "amnesic aphasia" did not involve either Broca's area or Wernick's area. The interesting point here is that Pick attributed his case to "atrophy in the left inferior and middle temporal gyri and to the sparing of Wernick's area", Graff-Radford., *et al.* [25]. Ironically enough, Pick's original description of pathology and lesion sites resembles today's description of AD (NOT Perusini's description of his single case, Auguste), especially when (Primary) Progressive Aphasia is brought in to bear on varying dementias as the diseases, Graff-Radford., *et al.* [25]; Green J, Morris JC, Sandson J., *et al.* [27].

Since then, however, there have been many cases reported concerning Pick's disease involving a wide variety of anatomical sites and clinical symptoms, Green., *et al.* [27]; Holland AL, McBurney DH, Moosay J, Reinmuth OM [28]; Malamud N and Boyd DA [29]; Kertesz A, Munzo D [30] with or without neurofibrillary tangles and with or without Pick bodies in the hippocampus.

As a result, the term "Pick complex", Kertesz [26], has now emerged in the literature to cover such a variety, only to be compounded by another term "fronto-temporal dementia or disease" (FTD) all because Pick complex or Pick bodies cannot be found in patients with FTD, because of territoriality. Such being the case, Pick's disease (PiD) has become less clear in terms of diagnosis without autopsied confirmation, because PiD, albeit rare, is often compared or contrasts with AD, even though AD is a fiction, when what should be dealt with or considered is the concomitant presence of the pathology of Fischer's disease (FD) in the form of Fischer's presbyophrenia.

In this sense, then, dementia in FTD (be it a disease or not) resembles that of atypical Parkinsonian disorders in terms of the appearance of dementia, except that FTD is otherwise said not to include Pick complex or Pick bodies but that atypical Parkinsonian disorders are said erroneously to include DAT (whatever that is).

Co-Morbidity of Fischer's Disease

For the aforementioned reason, let me now illustrate two things before I draw my conclusion: (1) a vivid example of the misdiagnosis of AD in a patient as reported by Caron Leid [31], because AD is a fiction; and (2) the main points of FD as characterized in Peng [3] to replace AD, because FD is likely to occur as a co-morbidity with PD for a comparison to verify two things:

1. Dementia in FTD is due to wear and tear on account of brain atrophy of whatever cause and dementia in atypical Parkinsonian disorders is also due to wear and tear, and thereby both dementias are not at all the result of a one-to-one cause-effect correlation but of a many-to-one cause-effect correlation.
2. If a concomitant pathology is or can be found in either FTD or atypical Parkinsonian disorders, I venture to claim that it is bound to be Fischer's presbyophrenia, the pathological substrate of which, as Fischer in 1907 and 1910 has already described, may turn out to be a mixture of plaques and tangles of either vascular or non-vascular origin.

My underlying construct of these two claims is that all brain diseases (or neurological disorders), be they of vascular or non-vascular origin, result in apoptosis which ensues in the brain dysfunctions of memory and cognition and varies in the rate of deterioration from

one form of neurological disorder to another as dementia. Such brain dysfunctions of memory and cognition also vary from person to person in terms of the age of onset and variety of symptoms. Here is another illustration besides the example *in vivo* already illustrated in Peng [2].

Resemblances of the Stages of Misdiagnosed AD and Fischer's Presbyophrenia

"Forgetful" early stage

- insidious/gradual
- recent memory loss
- time/space disorientation
- mood swings
- slower/withdrawal/denial
- impaired judgment
- subtle language dysfunction
- continues to worsen

"Confusion" early middle stage

- obvious memory deficits
- need for supervision in specialized activities
- language/communication problems
- anxiety/restlessness
- problem behaviour becomes more severe
- usually most difficult period for client

"Severe Dementia" stage

- obviously disabled cognitively
- full-time supervision needed
- marked personality/behaviour problems
- disorientation to person
- communication very difficult
- psychosis
- physical disorders appear
- can still reminisce

"Terminal" late stage

- almost total loss of intelligence/physical functioning
- few words spoken/understood
- emaciation/susceptible to infection
- death

Fischer's Brief Description of Presbyophrenia

1. The cases without necroses are simple senile dementia with a simple decrease of all mental abilities.
2. Those with necroses are more or less downright presbyophrenia with confabulation and worse disorders of memory.
3. Indeed, especially those medical cases, which show the most numerous glandular necroses, distinguish themselves by a faster deterioration and particularly by various hallucinations.
4. Even though we do not have any specific mutations of the senile cerebral cortex, we have to acknowledge the glandular necroses as the essential pathologic-anatomical substrate.

Take note that Fischer could not have described in 1907 and 1910 the day-to-day observations of the cases individually. But he vividly reported the main characteristics of simple dementia and downright presbyophrenic dementia. The comparison in similarity to watch is this: The Forgetful Early Stage corresponds to Fischer's Simple Dementia; and the "Terminal" Late Stage corresponds to Fischer's Presbyophrenic Dementia. The two stages in between, "Confusion" Early Middle Stage and "Severe" Dementia Stage, characterize vividly the progressive deterioration of proliferation in Fischer's dichotomy from simple dementia to presbyophrenic dementia.

At this point, I should commend the author, Ms. Caron Leid, for her careful observations and vivid description of her mother's behavioral alterations, which must have been quite painful to her, having to also take care of her newborn child. However, if there is any consolation to her disappointment, I regard her observations and description as constituting a significant contribution to the deteriorating credibility in neuroscience owing to the wild good chase on AD and new inventions of terminology.

Conclusion

In view of my provocative investigation stated above, and result of literature review, I wish to go one step further that any damage to the nervous system, be it vascular or nonvascular in origin, is bound to ensue in apoptosis; my view is based on my theoretical construct that the nervous systems are structurally interrelated and functionally interdependent. Examples are Multiple Sclerosis (MS), Epilepsy, PSP, SCA, HD, ALS, and many others. But there is a hidden catch: what investigators should watch out is the appearances of differing terminologies. For instance, Fischer uses the term plaques (or miliary foci) in 1907 and 1910 but Redich uses the term sclerosis in 1892, referring to the same brain pathology. For the clarification, see Peng [2].

What I want to emphasis here is that even in the 21st century, the term sclerosis still appears, as in MS and mesial temporal tuberous sclerosis in TLE (temporal lobe epilepsy). But most investigators tend to think that each one represents a different brain pathology. However, I wish to point out that sclerosis in MS is taken to mean scars [32]. Will epileptologists accept the same meaning for mesial tuberous temporal sclerosis in TLE or any other form of epilepsy wherein sclerosis also appears, for instance, frontal lobe epilepsy in extra-TLE or limbic epilepsy?

Take note, however, that both tuber and miliar characterize or describe the shape of what the viewer sees in a microscope, with the former referring to the shape of a lump or joint of a plant in botany, while the latter referring to the shape of a chestnut. Since different investigators in differing time and space view the same pathological object differently, by means of different languages to describe it, I wish to caution that the reader should not be misled to think that they characterize different pathologies.

Such being the case, let me (1) point out further that if sclerosis means neuropathologically a "scar" to MS experts, what is the connection between plaques and tangles in Fischer's presbyophrenia, and (2) speculate whether or not plaques or sclerosis may also appear in PD. Bear in mind, however, that Lewis Bodies may occur in patients with PD as well to result in dementia with Lewis Bodies (DLB). Therefore, let me quote a few passages from the pathology of MS commonly known in the literature, regarding the terms, plaques and sclerosis:

1. Known as plaques, these areas of thick tissue formed by the astrocytes show up as white patches on MRI exams.
2. The changes in size, number, and location of these plaques may determine the type and severity of the patient's symptoms as well as give the physician a visual chart by which to measure the progression of the disease.
3. Plaques may affect one axon or span across several.
4. They vary in size from that of a pinhead to more than an inch in length.
5. As plaques accumulate or increase in size, the functioning of the CNS deteriorates
6. Plaques as such are often widely distributed throughout the brain and spinal cord, many of which causing no apparent problems.
7. The term "multiple sclerosis" originates from the discovery of these plaques. Multiple refers to many; sclerosis refers to scars.
8. Inflammation does not always result in damage to the myelin and the forming of plaques. Some completely recover with no signs of any interference.
9. What instructs the cells to form the plaque is still unknown
10. What keeps the plaque from forming in other instances is equally puzzling.
11. Th-2 cells appear and release anti-inflammatory cytokines, which may be one factor in stopping the damage.
12. Inflammation only occurs in early stages of SPMS (Secondary Progressive MS), and later, primary degeneration causes the myelin and axons to become damaged. At this time apoptosis takes place, and cells simply die off. The latter is true for the other types of progressive MS as well, e.g., PPMS (Primary Progressive MS), PRMS (Progressive Relapsing MS), Malignant or Fulminant MS
13. A small subgroup of individuals with RRMS (Relapsing Remitting Form of MS) may follow a relatively benign course, still doing well –with little or no disability – after 20 years with the disease.

Given these quotes from MS, let me point out that apoptosis is the central issue for causing dementia. However, when reaching the stage of apoptosis, in the case of MS, note that plaques in MS change size and number once they are formed. I wish to point out that Fischer in 1907 described in great detail the same changes as follows:

- The smallest foci appear each in a round and spheroidal shape with a diameter of 10 - 20 μ . The bigger plaques, next in size compared to the last plaques, consist of a similar central part, with a broad circular ring of 15 - 25 μ . The next bigger plaques which are usually of the size of 60 - 80 μ , rarely of 100 - 120 μ , appear in a shape that evokes the image of an actinomicin geode.

Although Fischer was not sure of the neuropathological substance of the various sizes of plaques, experts in MS now identify it as caused by the astrocytes which increase in number and size, forming thick, dense tissue together with the other cells in the same area. This process creates firm tissue along the axons and is similar to a scar" [32]. I may therefore venture to postulate that when such first tissue is created in the bed of neuropils along the axons, it invades them, becoming neurofibrillary tangles. This invasion of plaques upon axons thereby prompted Fischer to claim: "There were no cases with tangles without plaques", suggesting that plaques and tangles might be two phases of one pathogenesis, as I have pointed out [3].

Such being the case. I wonder some of Fischer's cases might have MS, a neurological disorder not yet known in the early 19th century-before 1868 – although in 1868 Jean-Martin Charcot "was able to advance the understanding of several chronic diseases, including MS. Here is what he did.

In his 1868 description of the disease, Charcot describes plaques of demyelination and suggests the involvement of myelin in the development of MS. Charcot is also responsible for giving MS a name 'sclerose en plaque'. Although doctors at that time were familiar with the illness, Charcot provided a clear definition of the disease – so other doctors could more readily recognize and understand the condition.

Jean-Martin Charcot, born in Paris, 1825, was a French neurologist and professor of anatomical pathology. He is known as the “founder” of modern neurology. I presume that Fischer's approach must have been somewhat influenced by Charcot.

Given this historical fact of MS and its pathological characteristics involving myelin, it is conceivable to suggest that some of Fischer's cases which developed plaques or even miliary foci (early forms of plaques) had the involvement of myelin, albeit not necessarily developing into MS. That is, those patients in Fischer's samples did not develop MS but their plaques clearly had the pathological involvement of myelin to result in demyelination which affected neuronal axons but did not spread to become “multiple”. Put differently, patients of these cases developed, instead, neurofibrillary tangles intracellularly early on, as glandular necroses, albeit involving myelin as well, to become presbyophrenic before expiration.

The comparison made above is intended to show three things: (1) there is no Alzheimer's disease, e.g., DAT, in any patients with dementia; (2) when such patients are said to have AD, they are de facto misdiagnosed, as the case illustrated above; and (3) most likely they have towards the end Fischer's presbyophrenia because of apoptosis of whatever pathological origin, as evidenced by the case illustrated above.

However, at the beginning, each brain disorder affects the patients differently in terms of behavioral alterations. In the case of PD, all patients will show symptoms of (a) resting tremors, (b) gait disturbances, and (c) micrographia, among others; gradually they develop on-off phenomena; that is, with medication the on-phenomenon appears so that the patient may behave “normally”, but when the potency of medication wears off, the patient becomes stiff, motionless, and mute.

But if DLB is added as co-morbidity, different symptoms will appear, including (a) fluctuating alertness, (b) hallucinations, (c) excessive movement during sleep, and (d) depression, among others, all because of the worsening of apoptosis which starts from subcortical structures to cortical structure and gets worse every day to become eventually Fischer's presbyophrenic dementia.

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