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Complex liaisons moving forward the Parkinson's disease? An appraisal

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ABSTRACT

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder (ARND). Clinical signs of the disease can manifest decades after the onset of the molecular cascades promoting dopaminergic (DAergic) neuron loss. These however provide only a snapshot of the complex clinical pictures related to the disease. As a tip of an iceberg, subclinical events progressively emerge towards neurodegeneration as a result of the synergistic contribution of an array of environmental and intrinsic factors lurking beneath the waterline; early exposures to environmental hazards may predispose to the disease by advancing age. As a broader understanding of the mechanisms underpinning the disease might pave the way to better-tailored and timely-effective interventions, further knowledge urges on these issues. On the basis of an holistic perspective several tracks about risk and protective factors and their possible biological implications contextually to the onset of PD are hereby discussed.

Contents

1. Introduction

Epidemiological reports have recorded a steady increase in brain diseases worldwide [1–6]. In 2010, the estimated total cost of brain diseases was €798 billion in Europe [7] (Fig. 1). After Alzheimer's disease (AD), PD is the second most recurrent ARND with prevalence rates of 1–2% and 4% in over-65s and over-85s, respectively. Hereditary forms account for the ~10%, whilst the majority of cases manifests as a late-onset sporadic disease. The clinical hallmarks comprise a broad set of motor and non-motor features with a large impact on the patient's life quality as a result of the progressive loss of substantia nigra pars compacta (SNpc)

Abbreviations: ARND, age related neurodegenerative diseases; AD, Alzheimer's disease; ALS/PDC, amyotrophic lateral sclerosis-Parkinsonism dementia complex of Guam; BBB, blood brain barrier; BMAA, β-methylamino-L-alanine; CNS, central nervous system; CSF, cerebrospinal fluid; DA, dopamine; DAergic, dopaminergic; EFE, electromagnetic fields exposure; LB, Lewy's bodies; NMDA, *N*-methyl-D-aspartate; NR2B, NMDA-receptor 2 B; PD, Parkinson's disease; RFE, radio frequency exposure; SNPs, single nucleotide polymorphisms; SNpc, substantia nigra pars compacta; UA, uric acid.

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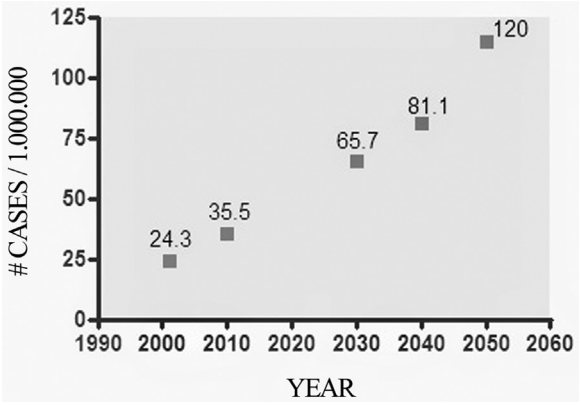

Fig. 1. Prevalence of brain disorders worldwide. This graph is an estimate of the data collected in [2] Dorsey et al. 2007, [6] Prince et al. 2013, WHO (http://www.who.int/mental_health/neurology/chapter_2_neuro_disorders_public_h_challenges.pdf) and world Alzheimer's reports (http://www.alz.co.uk/research/world-report). The global incidence rate of brain diseases is currently estimated of 4,6 million new cases/year, and is expected to double by twenty years. The prevalence of brain diseases is expected to exceed 100 million people by 2050. Misdiagnoses along with limited access to health care system could also impact the accuracy of epidemiological estimates.

neurons producing dopamine (DA) [8–11]. Apart from specific hereditary tracts, a litany of modifiable factors are also involved in the disease onset (Fig. 2). In light of basic science studies, clinical trials and epidemiological studies the putative neuroprotective and neurotoxic contributions of several genetic and environmental "hotspots" in the context of the PD are hereby discussed.

2. Brief glance at the genetic and molecular background of the disease

An increasing number of genetic tracts have been linked to PD [12–30] (Table 1). Among these, snca gene codifying for α-synuclein (aSyn) is detectable in patients' SNpc post-mortem [31,32], in the Lewy's bodies (LB) along with a variety of other proteinaceous precipitates. LB occlusions are observed in different neurodegenerative disorders as well as in gastrointestinal anomalies (§8). Other evidence pertaining to snca overexpression and

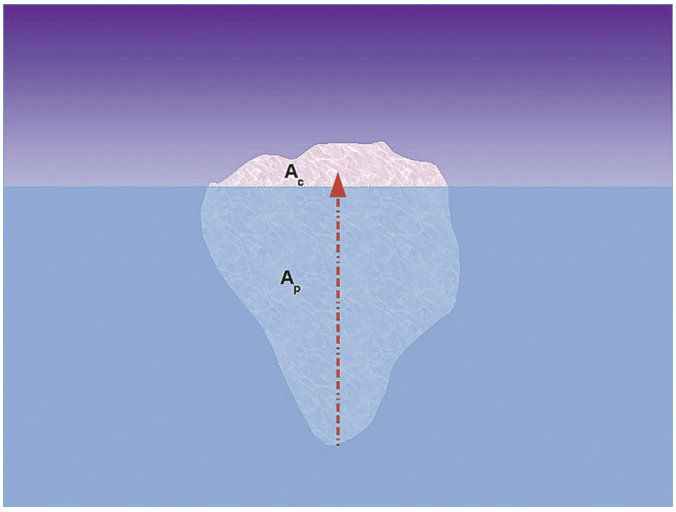

Fig. 2. The iceberg model of the Parkinson's disease. As the tip of an iceberg, the clinical events observed in the conclamated disease (Ac) only represent a minimal part of the complex liaisons underneath neurodegeneration. Taken from an holistic perspective, the driving force (f) towards this dynamic process is given by the summation of an array of environmental and intrinsic factors lurking beneath the waterline ($\int$ Ap).

enhanced aSyn accumulation are also consistent with a dose-dependent disease severity [33,34]. In LB, about 90% of the protein is post-translationally phosphorylated at S129; in yeast, this has been proven to modulate aSyn clearance [35]. The key role of chronic oxidation in the context of the PD is particularly evident in early-onset forms where the persistent neuro-oxidative environment generated by hereditary mitochondrial pathologies and lysosomal dysfunctions contributes dramatically to the disease progression [13,16,17,36,37]. Mutations in ATP7B sequences codifying for ceruloplasmin and leading to decreased synthesis of this copper transporter are described in ARNDs [38–42].

Another area of concern is the involvement of apolipoproteins in neurodegeneration. Unlike AD, PD it is not clearly associated with a distinctive plasma cholesterol profile. ApoA1, pivotal in the regulation of cholesterol transport and inflammation, is often found highly oxidized [43], and decreases in the cerebrospinal fluid (CSF) of PD patients [44,45]. ApoE, involved in lipid transport and injury repair in the brain, has gained consensus as a risk factor in AD [46], however discordant findings fuel debate on its role in PD [47]. Also, whether ApoEε4 may increase in the CSF of PD patients remains uncertain [48,49].

A set of epigenetic alterations has been associated with worse prognosis, e.g. DNA hypomethylation in CpG regions upstream to aSyn codyfing sequence [50–53], aberrant hypomethylation in parkin and reduced TNF-α synthesis [54,55]; also, epigenetic alteration for seven major human clock promoter regions have been highlighted [56]. Likewise, single nucleotide polymorphisms (SNPs) on IL-6 codifying region, in IL-1β, IL-10 and in IL-18 have been also described [57–61]. Significant associations between SNPs mapping in the vitamin D receptor region and disease risk are also reported [62,63]. Functional and regulatory polymorphisms of the poxonase gene also differentially contribute to disease risk in a dose-dependent fashion with regard to the gene expression [64]. Observations from a case-control study totaling 351 cases and 363 controls from rural areas with extensive usage of organophosphates report a greater than 2 fold increase in disease risk among PON1-55 variant carriers codifying for the paraoxonase-1 enzyme compared with non-exposed wildtype or heterozygous genotype cohorts [65]. In that same geographical area, similar findings have been described by Lee et al. in a study totaling 287 cases versus 440 controls [66].

Murine studies have also evidenced that histone hyperacetylation in DAergic neurons leads to degeneration after exposure of the pesticide dieldrin [67]. A closer glance on similar findings will be given in the following section.

3. Pollutants exposure

A growing body of evidence suggests a role for diverse environmental pollutants and metal-induced oxidative stress in PD aetiology. Increased lead [68,69], zinc [70] and other heavy metals favor free radical formation and neurodegeneration [71,72]. DAergic neurons result sensitive to the metal-induced oxidative stress. Increased plasma iron shows positive correlation with marker of lipid peroxidation as MDA [69]. Iron abnormalities increase the probability of developing AD when accompanied by hepatic distress [41]. Also, iron overexposure leads to nigral iron deposition [73–75], which determines a local increase in uric acid (UA) levels for protecting DAergic neurons [76,77]; however, in the SNpc of PD patients this powerful antioxidant decreases dramatically [78].

Copper overload increases aSyn expression and misfolding [79,80] and is involved in vasculopathies by down-modulating angiogenesis processes in AD and PD [81].

A pathological condition known as "manganism madness" due to manganese overexposure can be detected in welders with