ON THE ROAD TO THERAPEUTICS: BIOLOGICAL MECHANISMS OF PARKINSON'S DISEASE AND ALZHEIMER'S DISEASE

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ABSTRACT

This paper has sought to explore and summarise more recent findings on the genetic underpinnings of Parkinson's disease (AD) and Alzheimer's disease (AD). Recent studies have contributed to our understanding of these two devastating diseases. As the most common neurodegenerative disease, AD accounts for about two thirds of cases of dementia – ranging in various studies from 42 to 81 per cent of all dementia – with vascular causes and other neurodegenerative diseases such as Pick's disease and diffuse Lewy-body disease constituting the majority of the remaining cases. Meanwhile, it has been identified that PD is the second most common neurodegenerative disorder, after AD. The cause of PD remains unknown, but epidemiological studies suggest an association with pesticides and other environmental toxins, and biochemical studies implicate a systemic defect in mitochondrial complex. In light of the current findings and issues on PD and AD, this paper highlights the range of therapies available for those afflicted with these diseases.

Keywords: Alzheimer's Disease, Parkinson's Disease, Therapeutics, Dementia, Neurodegenerative Disease.

INTRODUCTION

The news is full of reports about dementia and its devastating effects. For instance, it has been reported last March of the previous year that rates of dementia in the Isle of Man is on the rise (BBC, 2014). When asked, most people have a particular fear of losing their mental faculties to dementia, over and above falling victim to other age-related conditions. Dementia is therefore a condition that everyone can relate to – particularly in the light of increased longevity – which exposes more and more people to chronic degenerative illness. By contrast, PD, an equally devastating chronic degenerative condition (de Munter, Melamed, & Wolters, 2014) which affects elderly people seems to enjoy a much lesser profile in the media and in the popular imagination in part because it is popularly associated more with physical motor symptoms and less with the loss of high end cognitive function that contributes to the essence of a sufferer's personality and character.

Dementia is an umbrella term used for neurodegenerative disorders, which is characterised by progressive loss of structure and function of neurons, often resulting to cell death. Neurons are cells that deliver information through chemical and electrical signals which controls movement, decision making and high-level brain function including memory. Unfortunately, dying neurons are not readily replaced; as a result their loss can be very damaging, resulting in a progressive loss of cognitive function and physical capacity. Neurodegenerative disorders can be both hereditary and intermittent, which makes the condition even more challenging to sufferers and their families.

There are several kinds of neurodegenerative disorders such as (PD), (AD), Huntington's disease, and motor neuron disease (also known as Amyotrophic lateral sclerosis). However, this paper aims to discuss the contrasting and comparing the biological pathology and underlying causes of PD and AD.

Objectives

In light of the issues pointed above, the present study aims to identify the following:

- Who gets afflicted with these diseases?
- What triggers these disorders?
- What are the symptoms and diagnoses?
- What are the underlying causes?

- What are the available treatments?

Who Gets Afflicted?

Both PD and AD disorders are prevalent among the elderly. It is considered that neurons become vulnerable as people age (Clegg, Young, Iliffe, Rikkert, & Rockwood, 2013). Neurons play an important role in the development of PD. Those neurons that are crucially involved in PD are associated with the substantia nigra, a structure situated in the midbrain. This structure is mainly responsible for movement and coordination. A recent study (Reeve, Simcox, & Turnbull, 2014) has demonstrated that in PD, the dopaminergic neurons of the substantia nigra increased the risk with advancing age. Aside from those damages, it has also been observed that there is a substantial decline in vital processes for the function of substantia nigra neurons, dopamine metabolism, wild type mitochondrial DNA copy number, and protein.

The substantia nigra is the part of the brain that is responsible for movement, addiction and reward (Rabey & Hefti, 1990). The decline in the function of the substantia nigra is often characterised by stiffness, tremor, bradykinesia and akinesia which are the most common symptoms of PD (Jankovic, 2008) .

By contrast AD is associated with increasing deposits of amyloid-beta (Aβ or A beta) – which are amino acids – in the brains of sufferers. These amino acids are thought of as the major component of the amyloid plaques observed in the brains of patients suffering with AD. A recent study on AD (Kövari, Herrmann, Bouras, & Gold, 2014) has indicated that amyloid deposition is increasing in ageing brains.

Amyloid plaques associated with AD are thought to impair functions by inhibiting the electrical conductivity and the action of acetylcholine in the neurons. Consequently the messages get slowed down or blocked.

What Triggers These Disorders?

Brain injury

In spite of what the previously mentioned studies suggest, neurodegenerative disorders – particularly PD and AD – may not be simply attributed to ageing. There are other factors that could also contribute to the development of having PD and AD. For instance, although such disorders are widespread to older people, there have been recent evidences (e.g. Gardner & Yaffe, 2014) that traumatic brain injury may increase the risk of early onset dementia.

One investigation (Marras et al., 2014) involving 65 cases of mild traumatic brain injury revealed that there may be an important causal relationship between brain injury and PD. Meanwhile, it has been proven in another experiment on causative factors in AD (Sawmiller et al., 2014) that it was shown that traumatic brain injury in mice delivered through a gas-driven shock tube device, significantly increases b-amyloid deposition glycogen synthase-3 (GSK-3) activation, phospho-tau, and pro-inflammatory cytokines (chemicals which appears in large amounts in patients with AD).

Environmental factors

It is known that PD is characterised by the inability of the brain to produce enough "dopamine," a neurotransmitter that is responsible for mood and for regulating movement. However, there are earlier findings that suggest a causal link with pesticides and other harmful environmental toxins (e.g., Greenamyre, 2000).

Recently, there are also increasing amount of evidence (e.g., Allen et al, 2014; Costa et al 2014; Goldman, 2014; Louis, Michalec, Jian, Factor-Litvak, & Zheng, 2014; Kim et al., 2014) that support the past studies which asserts the link between air pollution and exposure to pesticides with the symptoms of PD. Studies suggest that this is due to substantia nigra and striatum (region of the brain which helps to coordinate motivation with body movement) being particularly susceptible to harmful agents such as chemicals, pollutants and metals.

Sleep disorders

The beneficial effects of good sleep with cognitive performance among the elderly have been widely demonstrated (e.g., Pace-Shott & Spencer, 2014). One interesting question then arises as to whether sleep disruption could also be another factor that could potentially trigger neurodegenerative disorders such as AD and PD?

In comparison to other neurodegenerative disorders, it has been observed that those patients afflicted with AD have

more pronounced sleep-wake disturbances compared to those of their healthy counterparts (Bonakis et al., 2013). However, there is limited literature and research on the linkages between patterns and amounts of sleep and the development of PD. Risjman and his colleagues (2014) have explored the restless legs syndrome (RLS) and PD and ultimately they have found out that these two disorders can co-exist. Additionally, they have also explored whether or not these two disorders share a common pathophysiology. It was one of their findings that as PD progresses, nocturnal disturbances become even more noticeable, in association not only with motor symptoms but as well as with non-motor symptoms.

Genetic predisposition

The main known risk factor for PD is age. However, research has identified susceptibility genes such as synuclein, leucine rich repeat kinase 2 (LRRK-2) and glucocerebrosidase (GBA) which suggest that genetic predisposition is another essential causal factor.

Dopamine replacement therapy significantly reduces motor handicap, and effective treatment of constipation, nocturnal difficulties, pain, and associated depression can considerably improve the quality of life of PD sufferers. Moreover, gene therapy and embryonic stem cells are likewise showing promising results (Lees, Hardy & Revesz, 2009).

Meanwhile, the National Health Service (NHS), a publicly funded healthcare system in the UK describes AD as caused by regions of the brain wasting away, a process known as atrophy. Results to a multiplicity of damages in the structures of the brain. It is not known exactly what causes this process to begin, but people with AD have been observed to have unstable levels of amyloid plaques and tau tangles present in the brain. As a result, this reduces the effectiveness of healthy neurons, gradually damaging them. Over time, this loss spreads to other regions of the brain, including the grey matter, which is mainly responsible for processing thoughts as well as the hippocampus, which plays an important function in memory (NHS, 2012).

Diet

Studies looking at other potential factors that could trigger dementia are ongoing. Such findings are shedding further lights on our understanding of the nature of this disorder.

A recent study (Cai et al., 2013) reveals that advanced glycation end (AGE) food products affect the chemistry of the brain and consequently cognition. AGE is released through frying meat in pan, oven or grill. It is a byproduct when fats or proteins react with sugar, which happens during the cooking process. The result of this study is quite alarming as frying foods is a very common method of cooking.

The experiment involved feeding mice with AGE-based foods and the researchers found out that those mice that consumed low levels of AGE-based foods were able to prevent the building of damaged amyloid. On the contrary, when the levels of AGE have been increased the mice performed poorly in both thinking and physical tasks. The study further discusses their observation among people over 60 that the decline in their cognitive abilities is linked with high levels of AGES in their diets.

Symptoms and Diagnoses

Symptoms of PD are mainly movement-related (e.g., tremor, rigidity, stiffness, etc.) although there are also non-motor symptoms such as depression, apathy, sleep disorders and even erectile dysfunction (Chaudhuri & Schapira, 2009). Tsai and his colleagues (2014) explained that depression and neuropsychiatric symptoms are common to Parkinson's disease with Dementia (PD-D) rather than just PD. These cognitive issues are the primary symptoms however of AD, which further include memory loss, confusion and poor judgement, among others. But PD patients may also exhibit cognitive problems even without dementia, issues which are akin to those of AD. At present, there are no biomarkers capable of identifying those at greatest risk of developing PD-D (Duncan, et al., 2013).

AD is a specific diagnosis, named after Alois Alzheimer, a German psychiatrist who discovered it in 1906. AD is characterised by difficulty remembering events, confusion, aggression, and mood swings among others.

In contrast, the blanket term dementia refers to a whole range of cognitive symptoms that have a range of possible causes. AD can be confirmed through a series of brain scans, cognitive-behavioural assessments, and autopsy. Furthermore, Alzheimer's Society (2014), a UK-based

organisation working for people with dementia, explains that diagnosing dementia is often difficult, particularly in its early stages. Assessments can include conversations with the patient along with their relatives, carer, and friends; a physical examination; memory tests; and brain scans.

According to the Alzheimer's Society (2014), it is the Mini Mental State Examination (MMSE) which is the most recognised test used to identify the presence of memory problems or when a diagnosis of dementia is being suspected. It must be noted however, that becoming forgetful per se does not necessarily mean that one is afflicted with dementia. Memory loss can be a result of ageing. It can also be triggered by depression or stress. In rare instances, dementia-like symptoms can be due to brain tumour or vitamin deficiencies.

A conclusive diagnosis of the cause of dementia can only be validated at post mortem or, in very few cases, through a brain biopsy. Recently however, it has been reported that a blood test can accurately predict the onset of AD. Researchers showed that testing levels of 10 fats in the blood could predict - with 90 per cent accuracy - the risk of the disease coming on in the next three years (Mapstone et al., 2014).

Underlying Causes

Although in AD, there is the emergence of plaques which contains the substance fibrillar beta-amyloid, there is no direct connection between the number and location of plaques and cholinergic neuron loss. Currently available evidence strongly supports the position that the precipitating event for this disorder is related to unusual processing of beta-amyloid (A beta) peptide, ultimately leading to production of A beta plaques in the brain (Jack, et al., 2010).

This loss has instead been more closely associated to a soluble form of beta-amyloid that can intervene with the production and release of acetylcholine, and disrupt the behavior of a chemical called nerve growth factor that is involved in maintaining the structure and function of cholinergic neurons. There is also evidence that suggests that damage can be caused by the immune system reaction to the initial production of fibrillar beta-amyloid, before plaque formation, that involves the release of harmful chemicals (Jack, et al., 2010).

Treatments

Acetylcholine

The neurotransmitter acetylcholine is essential for judgement and learning but this is subsequently loss in AD. Combination therapy (with the N-methyl-d-aspartate receptor antagonist, memantine, and an acetylcholinesterase inhibitor) can be used however for the treatment of AD (Parsons, Danysz, Dekundy, & Pulte, 2013).

In contrast, acetylcholine in PD is in stable supply but due to the decrease in dopamine and the slower response time, the homeostasis required for normal movement is disrupted. Acetylcholine acts as an excitatory neurotransmitter and causes the muscles to contract while dopamine sends the message to relax. However, this seemingly simple process does not take place in PD. The striatal dopaminergic system, which is especially at risk to neurodegeneration for this disorder, appears to be the key contributor to these motor problems. However, numerous other neurotransmitter systems in the striatum are most likely to also play a significant role, including the nicotinic cholinergic system (Quik, et al., 2009).

With the onset of (PD), drugs such as dopamine agonists and levodopa can remedy its symptoms (National Collaborating Centre for Chronic Conditions, 2006). However, these are not panacea and cannot slow down its progression.

Patients suffering from PD have lower levels of a chemical known as gamma-Aminobutyric acid (GABA), in region of the brain known as the subthalamic nucleus. In one study (LeWitt, 2011), researchers have developed a virus which contained glutamic acid decarboxylase (GAD) that aids in producing GABA.

Sixty-six patients aged 30-75 years were recruited at seven centres in the US from 2008-2010 if they manifest symptoms of advanced PD for a minimum of five years and had not received previous brain surgery. To ensure valid diagnoses, scans were carried out. Unusual cases of PD and patients with dementia were excluded. Also, some patients were excluded if the inserted tube on their brain could not be correctly located or if the injection

malfunctioned. Consequently, this left 23 patients who were randomly assigned to receive placebo dose, and 22 were randomly assigned for gene therapy. Of these, 21 patients from the placebo group, and 16 patients from the treatment group, were considered for the final analysis.

This study explains the change of score from a rating scale called Unified Parkinson's Disease Rating Scale (UPDRS) which is used to measure the progression of PD. This randomized double-blind clinical trial of gene therapy for PD has met its foremost aim of improved UPDRS motor score at six months, and raised no crucial health and safety concerns.

Coffee

Extensive studies involving parkinsonian animals (i.e., rodent models) show that nicotine protects against nigrostriatal damage. In turn findings such as this may help explain the well-established decline in PD incidence with tobacco and nicotine consumption. In addition, recent work shows that nicotine can reduce L-dopa-induced abnormal involuntary movements, which is a weakening complication of L-dopa therapy for PD. These combined findings indicate that nAChR stimulation may pose a beneficial treatment strategy for PD to Further enhance neuroprotection and symptomatic treatment (Quik, et al., 2009).

Furthermore, some studies (e.g. Ludwig, Clifford, Lean, Ashihara, & Crozier, 2014) show that phytochemicals found in green coffee beans could also potentially help in alleviating the symptoms of PD. It has been explained that key compounds in the coffee beverage, produced from the ground, roasted beans, have essentially beneficial impact to neurodegenerative disorders.

Dancing and exercise

PD is a progressive movement disorder that is frequently characterised by poor coordination such as impaired balance and walking. But more recent studies indicate that dance (Earhart, 2010) and exercise (Dibble, Addison, & Papa, 2010) may be effective alternative treatments addressing these areas of concern to patients with PD. There are also studies (e.g., Lewis, Annett, Davenport, Hall, & Lovatt, 2014) which suggest that mood improves following social dance sessions in people with PD. It could be possible that dancing and exercise stimulates the release of dopamine.

Clinical approach

Currently, there is no known cure for PD, but there are medical treatments available including occupational, surgical procedures, pharmaceuticals, physical therapy. Although, the mainstay drug that is being used is still levodopa. By replacing dopamine, this drug can minimise the motor symptoms of the PD by replacing the dopamine. Levodopa is frequently combined with a peripheral decarboxylase inhibitor such as carbidopa. These drugs help by disabling side effects such as dystonia, and immobile rigidity, dyskinesias, but may also have neuroprotective factors (Davie, 2008).

In contrast, drugs such as galantamine, donepezil, and rivastigmine (which are AChE inhibitors) can be prescribed for patients with mild to moderate symptoms of AD. Memantine may also be prescribed for those with moderate AD who cannot take AChE inhibitors or for those patients suffering with severe Alzheimer's disease (NHS, 2012).

Discussion

The central goal of this article was to provide a synthesis of the current findings about PD and AD. It also aims to generate practical recommendations developed from the recent findings in order to address issues of early diagnosis, treatment, and ultimately the care management of patients.

AD also called as dementia generally develops among the elderly leading to loss of memory and cognitive functioning such as thinking, remembering and reasoning and behavioural abilities that disturb the daily routine of the affected people. Parkinsonism is a neurodegenerative disease with symptoms like tremor, rigidity and postural problems. Monoclonal antibodies produced only one single, specific type of cell and all have the same activity. It can be purified and infused in any organism to produce a desired effect. Recent research suggests that monoclonal antibodies designed to specifically target these misfolding proteins in soluble, aggregated states, may be ideally suited to treating neurodegenerative diseases.

Meanwhile, PD is a disorder of the nervous system that

affects your movement and mental ability. It develops gradually which is characterised by shaking in thumb, chin or lip, movements during sleeping, feeling dizzy and low blood pressure. PD cannot be cured for the meantime. However, in some cases, doctors may suggest medication, pharmacology treatment and surgery to rejuvenate certain regions of the brain. It has been revealed that anti-PD medication treatment can bring about a fairly effective control of PD for around five years. Physiotherapy can also be considered as an alternative treatment to improve your muscle strength.

Researchers have plans for further animal tests of their monoclonal antibody regimen, on its own and in combination with other approaches, before proceeding to clinical trials. AD, along with other dementias affects 47 million people worldwide and millions of British people, trends that are expected to triple by 2050, according to the organisations. This surge is expected to put a tremendous strain on the healthcare system unless better screening and treatment methods are identified.

While it has been revealed that there were significant psychiatric differences between patients with AD and demented patients with PD, but neuropsychological differences were restricted to a single cognitive domain. The outward manifestations of growing older:grey hair, wrinkles, stiffening joints, slower response times and 'senior moments' - are as well-known as the many products advertised to address them, researchers still remain to know little about how people age. Yet the incentive to uncover the secrets of ageing is powerful: advancing age is the single greatest risk factor for most human diseases, from arthritis and cancer to diabetes and neurodegenerative disorders.

Recommendations

To address the complex needs of the patient with dementia and the caregiver during the course of a dementia disorder the specialist physicians should collaborate with other health care professionals with special training in dementia. The specialist physician should schedule regular follow-up visits, the purposes of which include: (1) to assess cognitive, emotional, and behavioural symptoms together with the functional status; (2) to evaluate treatment indications and to monitor pharmacological and non-pharmacological treatment effects; (3) to ensure identification and appropriate treatment of concomitant conditions and of complications of the primary dementia disorder; (4) to assess caregiver burden and needs; (5) to assess sources of care and support; (6) to provide continuous advice and guidance to patient and caregiver on health and psychological issues, safety measures, driving, and legal and financial matters, and (7) to administer appropriate patient and caregiver interventions. The primary caregiver, when available, should accompany the patient with dementia at follow-up visits and investigations (Waldemar et al., 2007). Additionally, it should be underscored that appropriate utilisation of antidementia therapy and care management is vitally important to achieving quality of life and care for dementia patients and their caregivers, and for managing the excess costs of AD. These recommendations address relevant, practical, and timely concerns that are faced on a daily basis by practitioners and researchers who continue to champion the cause of improving the care of dementia patients.

Conclusion

During the first few years of PD and AD, research focused on diagnosis, establishing the clinical levels and measuring progression and controlling symptoms. Many primary questions remain unanswered around their causes, and more importantly their treatments.

There are a number of therapies for PD which seems to be effective at mitigating the worst symptoms of the condition but still not able to predict its onset or assess vulnerability, nor can prevent or cure the disease.

By contrast AD is harder to diagnose less about the underlying causes although recent studies has made a significant contribution to predicting who might be at risk and raised the possibility of considering prophylactic therapy. AD is harder to generally treat and mitigate, Like PD, AD remains impossible to cure. With this in mind, researchers and academics should carry on collaborating to achieve more relevant and practical discoveries towards alleviating the damaging effects of these neurodegenerative disorders.

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