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Review

Emergence of breath testing as a new non-invasive diagnostic modality for neurodegenerative diseases

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ABSTRACT

Neurodegenerative diseases (NDDs) are incapacitating disorders that result in progressive motor and cognitive impairment. These diseases include Alzheimer's disease, the most common cause of dementia, frontotemporal dementia, amyotrophic lateral sclerosis, dementia with Lewy bodies, Parkinson's, Huntington's, Friedreich's ataxia, and prion disease. Dementia causing NDDs impose a high social and economic burden on communities around the world. Rapid growth in knowledge regarding the pathogenic mechanisms and disease-associated biomarkers of these diseases in the past few decades have accelerated the development of new diagnostic methods and therapeutic opportunities. Continuous effort is being applied to the development of more advanced, easy-to-apply and reliable methods of diagnosis, that are able to identify disease manifestation at its earliest stages and before clinical symptoms become apparent. Development of these diagnostic tools are essential in aiding effective disease management through accurate monitoring of disease progression, timely application of therapeutics and evaluation of treatment efficacy. Recently, several studies have identified novel biomarkers based on compounds in exhaled breath associated with specific NDDs. The use of breath testing, as a means of monitoring neurodegenerative disease onset and progression, has the potential to have a significant impact on augmenting the diagnosis of NDDs as the approach is non-invasive, relatively cost effective and straight forward to implement. This review highlights key features of current diagnostic methods utilised to identify NDDs, and describes the potential application and limitations associated with the use of breath analysis for disease diagnosis and progression monitoring.

Contents

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1. Introduction: Prevalence of neurodegenerative diseases

The number of people diagnosed and living with neurodegenerative diseases (NDDs) is steadily increasing because of increasing lifespan. The chance of developing a neurodegenerative disease increases dramatically with advancing age, doubling every 5–10 years beyond the age of 65 (Castellani et al., 2010; Ferri et al., 2005; Forman et al., 2004). A systematic review and meta-analysis proposed that an estimate of 35.6 million people worldwide were living with dementia caused by neurodegenerative disorders in 2010 (Prince et al., 2013). The prevalence is projected to approximately double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (Prince et al., 2013). An accurate prevalence of NDDs is difficult to estimate due to lack of large-scale epidemiological studies particularly in the developing world, and the use of non-standardised diagnosis criteria (Ferri et al., 2005). In addition to heightened social and mental burden, NDDs inflict a huge healthcare cost on society. The most common type of neurodegenerative disease, Alzheimer's disease, is estimated to cost $172 billion per year in the United States of America alone (Reitz and Mayeux, 2014).

Neurodegenerative diseases encompass a variety of debilitating, progressive disorders associated with neuronal degeneration (Ross and Pickart, 2004). The common types of NDDs include Alzheimer's disease (AD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), dementia with Lewy bodies (DLB), Parkinson's disease (PD), Huntington's disease (HD), Friedreich's ataxia (FRDA), and prion disease. Disease manifestation occurs predominantly in individuals above the age of 45 years old, (with the exception of FRDA where the common form results in onset between 5 and 15 years of age), although it is not uncommon for younger individuals to be affected (Bertram and Tanzi, 2005; Walker, 2007). General symptoms of NDDs include dementia, cognitive decline, motor impairment, behavioural transformation, psychosis and emotional disturbance (Bertram and Tanzi, 2005). Severity of symptoms gradually advances with disease development, resulting in deterioration of the capacity for independent living in affected individuals, and ultimately causing death (Brookmeyer et al., 2007; Helder et al., 2002). The typical disease course has a mean duration of 10–15 years from the onset of clinical symptoms, although there can be a large variability in disease duration amongst individuals, and there are currently no cures once symptoms have been established (Brookmeyer et al., 2007; Helder et al., 2002).

Neurodegeneration is a gradual process and is known to start 20–30 years before clinical onset (Davies et al., 1988; Potter et al., 2013). Progression of NDDs can generally be categorised into three phases; preclinical, mild cognitive impairment (MCI) and clinical phases (Petersen, 2004; Sperling et al., 2011). Although noticeable clinical signs are absent during the preclinical phase, there are gradual physiological changes at the cellular level associated with disease pathogenesis. At the MCI phase, early non-clinical symptoms of cognitive impairment will start to manifest, where individuals who are at increased risk of developing dementia experience noticeable, but not severe, cognitive alterations. The MCI phase is a transitional state between normal ageing and clinical onset of NDDs, such as AD (Petersen, 2004). Due to the insidious nature of NDDs, treatment will be most beneficial if applied before clinical symptoms become apparent (Sperling et al., 2011). Therefore, a biomarker that is able to reliably identify disease development at the preclinical phase has high clinical value because it not only allows for early diagnosis, but also provides an opportunity for application of early preventative treatments.

In general it is assumed that, early detection of NDDs is or will be important for timely application of preventative treatments and effective disease management. This review provides a comprehensive summary of diagnostic methods that are currently available for diagnosis of neurodegenerative disorders, including their key features such as function, diagnostic efficiency, advantages and limitations. In general, the accuracy of diagnostics is highly influenced by the type and validity of features or biomarkers being assessed, the genetics, where available being the most accurate. The characteristics and significance the known biomarkers for diagnostic applications of NDDs are summarised in this review. We also highlight the attributes of recently discovered novel breath testing biomarkers, and their current application in diagnosis of neurodegenerative disorders through breath analysis. Furthermore, the present review also discusses the feasibility, challenges and future direction of breath analysis as a diagnostic method in the field of neuroscience.

2. Diagnostic methods and biomarkers of neurodegenerative diseases

With the advancement of new potential treatments for NDDs, there is a fundamental necessity for the development of diagnostic methods that are able to objectively diagnose, measure and monitor changes related to disease pathogenesis and efficacy of therapeutics. Characteristic features of the most commonly used screening tools for diagnosis of NDDs, and their respective advantages and limitations are summarised in Table 1. Traditionally, neuropathology is considered as the most precise method of clinical diagnosis for NDDs, as it provides direct insight into the actual physical conditions of the brain (McKhann et al., 1984; Eskildsen et al., 2015). The major drawback to this diagnostic method is that it involves examination of brain tissue either from surgical biopsy intervention or whole-body autopsies after death, whilst surgery is a high-risk and invasive option for biopsy (Perl, 2010).

Neuropsychological assessment primarily evaluates aspects of cognitive activities such as premorbid activity, memory, intellectual, language, visuoperceptual, spatial, executive and attention functions (Bokde et al., 2011). Although neuropsychological assessment is highly sensitive, it has low specificity due to its limited ability to provide quantitative evaluation on progression of a specific disease (Bokde et al., 2011).

Neurophysiological assessment of NDDs generally refers to analysis of the brain's electrical signals, usually by electroencephalogram (EEG). Typical neurophysiological assessment is susceptible to contamination of "noise" during data acquisition, and diagnosis is very subjective due to its dependence on evaluation of EEG data through visual inspection by a trained expert. However, EEG recordings can be reviewed to find epochs of artefact-free data, and only 60 s of artefact-free data is required for most quantitative EEG applications (Hargrove et al., 2010). In addition, automated tools based on mathematical algorithms are currently available for isolating artefacts to overcome problems associated with visual inspection and result interpretation (Delorme et al., 2007; Junghofer et al., 2000; Mognon et al., 2011; Nolan et al., 2010).

Neuroimaging is the most commonly used *in vivo* assessment of brain structure and volume for diagnosis of NDDs in clinical applications (de Haen, 2001; Ferreira and Busatto, 2011; Higuchi et al., 2005). Neuroimaging can be divided into two categories; structural imaging and functional imaging. Structural neuroimaging provides detailed two- or three-dimensional brain topography, and includes techniques such as computed tomography (CT) scan, magnetic resonance imaging (MRI), diffusion-and-perfusion-weighted magnetic resonance imaging (DWI- and PWI-MRI), and diffusion tensor magnetic resonance imaging (DTI-MRI) (Bokde et al., 2011; Brenner and Hall 2007; Ferreira and Busatto, 2011). Functional imaging, however, provides information on the functionality of brain tissues by observing tissue metabolic activity (Bateman,