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Gait dyspraxia as a clinical marker of cognitive decline in Down syndrome: A review of theory and proposed mechanisms

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ABSTRACT

Down syndrome (DS) is the most common genetic cause of intellectual disability in children. With aging, DS is associated with an increased risk for Alzheimer's disease (AD). The development of AD neuropathology in individuals with DS can result in further disturbances in cognition and behavior and may significantly exacerbate caregiver burden. Early detection may allow for appropriate preparation by caregivers. Recent literature suggests that declines in gait may serve as an early marker of AD-related cognitive disorders; however, this relationship has not been examined in individuals with DS.

The theory regarding gait dyspraxia and cognitive decline in the general population is reviewed, and potential applications to the population with individuals with DS are highlighted. Challenges and benefits in the line of inquiry are discussed. In particular, it appears that gait declines in aging individuals with DS may be associated with known declines in frontoparietal gray matter, development of AD-related pathology, and white matter losses in tracts critical to motor control. These changes are also potentially related to the cognitive and functional changes often observed during the same chronological period as gait declines in adults with DS. Gait declines may be an early marker of cognitive change, related to the development of underlying AD-related pathology, in individuals with DS. Future investigations in this area may provide insight into the clinical changes associated with development of AD pathology in both the population with DS and the general population, enhancing efforts for optimal patient and caregiver support and propelling investigations regarding safety/quality of life interventions and disease-modifying interventions.

1. Down syndrome and Alzheimer's disease

Down syndrome (DS, or trisomy 21) is the most common genetic cause of intellectual disability in children, which results from triplication of all or part of chromosome 21 (Dierssen, 2012; Lejeune, Gautier, & Turpin, 1959; Millan Sanchez et al., 2012). In addition to the well-established physical phenotype related to DS (Roizen & Patterson, 2003), DS carries increased risk for multiple clinical disorders, including congenital cardiac and gastrointestinal malformations, leukemias and immune disorders, as well as disorders of the endocrine/metabolic systems (Bull, 2011; Cenini et al., 2012; Lott & Dierssen, 2010; Roizen & Patterson, 2003). Individuals with DS also have an elevated risk for developing Alzheimer's disease (AD) as they age (Cosgrave, Tyrrell, McCarron, Gill, & Lawlor, 2000; Holland, Hon, Huppert, & Stevens, 2000; Lott & Dierssen, 2010; Lott et al., 2011). AD is the leading known cause of dementia in aging individuals (Reitz, 2012) and has been strongly associated with apolipoprotein E (APOε) genotype in the general population (Strittmatter & Roses, 1996). Further, APOε genotype appears to interact with the β-amyloid precursor protein (APP) (Bachmeier et al., 2013; Maloney & Lahiri, 2011). The markedly increased susceptibility to AD in DS (or DSAD) is thought to be related to the triplication of all or part of chromosome 21, resulting in overexpression of

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multiple genes implicated in AD, APP in particular (Lott & Dierssen, 2010; Rumble et al., 1989).

In the general population, the pathological changes associated with AD development, including Aβ production via APP cleavage, likely begin years before the onset of noticeable clinical symptoms (Sperling et al., 2011). Although this process is thought to begin in middle age in the general population, Aβ accumulation in people with DS can begin in childhood (Lott & Dierssen, 2010). This is followed by strikingly accelerated deposition and aggregation into senile plaques beginning at approximately age 30 in DS (Mann & Esiri, 1989). In fact, the accumulation of Aβ plaques and neurofibrillary tangles that follows is so rapid that nearly all individuals with DS have the pathological changes of AD by age 40 (Mann & Esiri, 1989; Wisniewski, Wisniewski, & Wen, 1985).

Not all individuals with DS show clinical signs of dementia despite established AD pathology on autopsy (Nieuwenhuis-Mark, 2009; Zigman, Schupf, Sersen, & Silverman, 1996), but when dementia is present, it is often characterized by disturbances in memory, apraxia, agnosia, and changes in personality with behavioral disorders (Lott & Dierssen, 2010). These cognitive disorders often result in markedly compromised functional skills, including basic activities of self-care such as feeding and bathing (Carr & Collins, 2014; Cosgrave et al., 2000; McKenzie, Murray, McKenzie, & Muir, 1998). As such, dementia in intellectually disabled (ID) individuals can significantly increase caregiver burden, as caregivers may not be prepared to meet the needs of loved ones with both ID and dementia (Bittles & Glasson, 2004). This highlights the critical practical value of detecting both cognitive and functional changes as expediently and accurately as possible. Accurate early detection can enhance care efforts as well as furthering understanding of the mechanisms driving such declines. If successful, such efforts can catalyze development of both population-appropriate compensation strategies and disease-based interventions for DSAD.

2. Gait and cognitive change

Along with the significant advances in amyloid imaging techniques and spinal fluid biomarkers as tools for early diagnosis of AD (McKhann et al., 2011; Neltner et al., 2012; Sperling et al., 2011), there is a growing body of literature from the general population suggesting that gait declines often emerge before other clinical symptoms of dementia. The association of disorders of gait with the development of dementia over time, suggests that the mechanisms underlying gait change and cognitive change may be closely related (Mielke et al., 2013). Specifically, although declines in gait speed and other motor skills are certainly expected throughout the typical aging process, gait disturbances beyond those expected with age have been associated with multiple types of dementing diseases, including AD (Sheridan, Solomont, Kowall, & Hausdorff, 2003) and different subtypes of Mild Cognitive Impairment (MCI) (Pedersen et al., 2014).

Mild Cognitive Impairment (MCI) refers to an early period of cognitive decline during which symptoms do not markedly hinder essential activities of daily living (Albert et al., 2011; Mura et al., 2014; Petersen, 2004). In AD, clinical dementia is often preceded by amnestic MCI, a disorder characterized by largely isolated episodic memory deficits. Subsequent conversion to dementia is determined clinically, when evidence for increasing cognitive and functional impairments are accompanied by objective evidence of a neurocognitive decline (McKhann et al., 2011; Sperling et al., 2011). Burrachio and colleagues demonstrated that individuals in the general population converting to MCI showed more rapid declines in gait compared to participants who did not convert to MCI, and this alteration in gait was observed more than a decade before the usual clinical signs of MCI emerged (Buracchio, Dodge, Howieson, Wasserman, & Kaye, 2010). In a different analysis involving a 7-year follow-up of 647 autonomously living older women, decreased gait speed was shown to be an independent risk factor for dementia after statistical adjustment for multiple demographic factors, including physical activity levels, comorbidities such as body composition, and self-reported disabilities (van Kan et al., 2012). Some studies have even reported that changes in balance and spatiotemporal gait parameters are more closely connected to cognitive decline in statistical models than chronological age (Achache et al., 2013). Thus, the successful identification of a gait disorder may help predict the onset of dementia in the general population.

To help detect those aging individuals who demonstrate gait decline as a predominant risk factor for cognitive decline, Verghese, Wang, Lipton, and Holtzer (2012) proposed the construct of Motoric Cognitive Risk syndrome (MCR). The development of the MCR was based on their findings regarding gait, cognition, and functional status from a cohort of 997 community-dwelling adults who were at least 70 years old. Their preliminary criteria for MCR include: (a) the presence of subjective cognitive complaints (b) without the presence of dementia on formal neuropsychological measures, (c) preserved activities of daily living, and (d) slow gait, demonstrated as gait speed one standard deviation or more below other peers in the cohort grouped by age and sex.

Though MCR is young in its conceptualization and validation, initial evidence suggested that individuals meeting criteria for MCR syndrome have more than a threefold greater risk of developing dementia of any type and greater than a twelvefold greater risk of developing vascular dementia (Verghese et al., 2012). A larger-scale investigation of 26,802 adults ages 60 and older from 17 different countries and 5 continents also indicated that individuals meeting MCR criteria (9.7% of the total sample) demonstrated significantly weaker cognitive performances than individuals who did not meet criteria (Verghese et al., 2014). These individuals also were at higher risk for worsened cognitive impairment and frank dementia at follow up, which occurred at least 5.1 years later in these participant groups. Beyond MCR specifically, disordered gait has also been associated with other practical outcomes, including falls (Hausdorff, Rios, & Edelberg, 2001) and overall mortality (Toots et al., 2013). If these patterns of gait and cognitive changes hold true for people with DS, then measurement of gait change may represent a straightforward, noninvasive method for illuminating underlying pathological and clinical changes related to both DSAD and AD.

3. Gait dyspraxia in dementia

The term "apraxia" was first used by (Steinthal, 1881) to describe the impairment of a patient's ability to correctly carry out motor programs. Steinthal suggested that apraxia is "...not that the movement ...of the limb is restricted, but the relation of the movement to the object to be handled; the relation of the movement to the purpose is disturbed...". Praxis requires the adequate operation of and successful integration of multiple cortical and subcortical regions, including the frontal and parietal cortices and their associated white matter tracts. Disruptions in praxis can hinder a variety of basic and complex skills, including volitional movements of the eyelids, mouth, and tongue, speech production, the ability to mime practical movements (like lighting a match or brushing one's teeth), and gait. Dyspraxias, including gait dyspraxias, are often observed in people with dementia in both the general population and in individuals with DS (Chandra, Issac, & Abbas, 2015; Dalton & Fedor, 1998).

Gait dyspraxia is characterized by diminished capacity to correctly use the legs for ambulation when this deficit cannot be attributed to sensory impairment, motor weakness, poor