4-17-2017

Orthostatic Hypotension in Individuals with Alzheimer's Disease: Case Study

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Abstract

Orthostatic hypotension occurs when a decline in blood pressure follows immediately after taking an upright position (Freeman et al., 2011). While more prevalent with age, those with Alzheimer's disease, a neurodegenerative disorder that is the leading cause of dementia, have an even higher prevalence of orthostatic hypotension (Alzheimer's Association, 2017; Sonnesyn et al., 2009).

This review examines and synthesizes the available evidence as it applies to a patient case, an elderly woman with dementia and hypertension who presented with fatigue and dizziness. Topics of focus include the prevalence of orthostatic hypotension, the etiology of orthostatic hypotension in Alzheimer's disease, the association with falls and orthostatic hypotension, and orthostatic hypotension as an adverse effect of atypical antipsychotic use.

The purpose of the review is to assist assisting practitioners in the diagnosis and management of these increasingly prevalent conditions in addition to identifying areas in need of further research.

Keywords: orthostatic hypotension, Alzheimer's disease, falls

Orthostatic Hypotension in Individuals with Alzheimer's Disease: Case Study

Background

Orthostatic hypotension, a clinical sign, refers to a decline in blood pressure when in an upright position and can either be symptomatic or asymptomatic (Freeman et al., 2011). Several neurocardiovascular mechanisms function to maintain blood pressure, and, therefore, adequate cerebral blood flow to vulnerable brain tissue (Perlmuter et al., 2012). Orthostatic hypotension represents a failure of these mechanisms to control blood pressure with the redistribution of blood volume that occurs with an upright position (O'Callaghan & Kenny, 2016).

The purpose of this review is to understand the link between Alzheimer's disease and orthostatic hypotension by synthesizing available evidence as it applies to a patient case. Understanding the associations between Alzheimer's disease and orthostatic hypotension from the evidence will assist practitioners in the diagnosis and management of these increasingly prevalent conditions. According to the Alzheimer's Association (2017), the prevalence of Alzheimer's disease is expected to greatly increase with the aging of the American population with an estimated 7.1 million cases of Alzheimer's disease in adults 65 years of age and older by 2025; this is a 35% increase in prevalence from 2017. Additionally, by synthesizing the available evidence, areas in need of further study will be highlighted.

Case Report

Patient: L.B. *Age*: 78 *Sex*: Female *Race*: Caucasian

Subjective

Chief Concern: Follow-Up after Hospital Discharge

History of Presenting Illness: L.B. is a 78-year-old female with a significant past medical history of dementia, major depressive disorder, chronic obstructive pulmonary disease, anemia, hypertension, type 2 diabetes mellitus, and peripheral neuropathy who presents to the clinic today unaccompanied for a follow-up after hospital discharge. L.B. was hospitalized for 3 days for a urinary tract infection and discharged with a seven-day course of Nitrofurantoin; she has three days remaining of antibiotic treatment. Prior to hospitalization L.B. experienced urinary urgency and dysuria, which is not present today. She reports feeling well today however does mention feeling dizzy, particularly with position changes, with associated lightheadedness, and fatigue. L.B. states these symptoms have been present for a year, are not particularly troublesome to her, and she often takes naps throughout the day to partially relieve her fatigue. L.B. feels the fatigue and dizziness have progressively worsened throughout the past year. She reports she has not fallen in the last year.

Pertinent Medical History

- Dementia
- Major Depressive Disorder
- Chronic Obstructive Pulmonary Disease
- Anemia
- Hypertension
- Type 2 Diabetes Mellitus

- Peripheral Neuropathy

Medications

- Donepezil 5 mg by mouth daily
- Quetiapine 200 mg by mouth twice daily
- Paroxetine 20 mg by mouth daily
- Fluticasone proprionate 250 mcg/ Salmeterol 50 mcg inhalation 1 puff twice daily
- Iron Sulfate 325 mg by mouth twice daily
- Multivitamin tab by mouth daily
- Metoprolol 50 mg by mouth twice daily
- Losartan 50 mg by mouth daily
- Insulin glargine 30 units subcutaneously daily at bedtime
- Gabapentin 300 mg by mouth three times daily
- Nitrofurantoin ER 100 mg by mouth twice daily for 7 days (3 days remaining)

Allergies: No known drug allergies

Family History: Dementia- Mother (deceased); Chronic Obstructive Pulmonary Disease- Father (deceased); Type 2 Diabetes Mellitus- Sister

Social History: L.B. lives in an assisted living facility where she receives complete assistance with medication management and some assistance with activities of daily living such as bathing. She is able to toilet and dress herself. Her daughter lives nearby and visits her on the weekends. She does not currently smoke, drink alcohol, or use illicit drugs. L.B. is a retired schoolteacher.

Review of Systems

Constitutional: Patient denies chills, fever, weight loss or gain, or insomnia.

HEENT: Denies vision changes, hearing changes, ear drainage or pain, throat pain, or trouble swallowing.

Skin: No new rashes or lesions.

Cardiovascular: No chest pain, pressure, or palpitations; No edema

Pulmonary: No cough, shortness of breath, or hemoptysis

Gastrointestinal: No heartburn, vomiting, nausea, diarrhea, constipation, melena, or bright red blood per rectum

Genitourinary: No dysuria, urinary frequency, or urinary hesitancy noted.

Musculoskeletal: No joint swelling or tenderness

Neurological: Denies headaches. Reports numbness and tingling to bilateral lower extremities.

Psychiatric: Denies depression or anxiety. PHQ-2 negative.

Endocrine: Reports her morning fasting blood glucose reading was 107

Objective

Vital Signs

BP 88/40 ! HR 50 ! RR 18 Temp 37 C

Physical Exam

General: Pleasant, cooperative, and fatigued-appearing female in no acute distress; Dizzy and lightheaded upon standing

Skin: No significant rashes or lesions noted

HEENT: Normocephalic; Sclera white and conjunctiva clear and non-apparent, pupils equal and round, EOMs intact to the six cardinal fields; No oral lesions, Uvula midline and rises to phonation

Heart: S1, S2 with a regular rhythm. Bradycardia. No S3, S4, murmurs, clicks, rubs, or gallops.

Lungs: Respirations non-labored and regular without accessory muscle use. No barrel chest. Equal chest wall expansion. Breath sounds clear and symmetric to all lung fields. No rhonchi, wheezing, or crackles.

Abdomen: Abdomen obese and soft without obvious masses. Active bowel sounds to all quadrants. No tenderness or masses present to light and deep palpation.

Extremities: No clubbing or cyanosis. Trace edema to bilateral lower ankles. Capillary refill less than 2 seconds. +2 radial pulses bilaterally; +1 pedal and posterior tibial pulses bilaterally.

Musculoskeletal: No joint swelling, tenderness, deformity, or erythema.

Neurologic: Alert, attentive, and oriented to person, place, time, and situation. Short-term memory deficits present. Cranial nerves II-XII are grossly intact. 5/5 upper and 4/5 lower extremity strength. Gait is unsteady with the use of a four-wheeled walker.

Psychiatric: Affect is consistent with situation.

Assessment/Plan

I95.9 Hypotension, unspecified

Comment: Likely due to adverse effect of medications, such as beta-blockers, or of cardiac etiology. Presence of symptomatology consistent with orthostatic hypotension makes this highly probable. Hypotension is unlikely due to fluid volume deficit or of infectious etiology due to bradycardia though this cannot be ruled out due to beta blockade.

- Obtain orthostatic vital signs
- Decrease Metoprolol to 25 mg by mouth twice daily
- Orders sent with patient to check vital signs tonight and tomorrow and to update me in the morning

- Education provided to the patient to make position changes slowly and to ensure adequate oral intake
- Follow-up appointment in 2-3 days

R00.1 Bradycardia, unspecified

Comment: Bradycardia with hypotension. Etiology thought to be likely related to above.

- Check a Basic Metabolic Panel
- Obtain an EKG now

D64.9 Anemia, unspecified

Comment: Progressive chronic fatigue with symptomatology consistent with orthostatic hypotension. Anemia, especially considering her positive past medical history of this diagnosis, could be contributory to her symptoms.

- Check a Complete Blood Count with Differential

Addendum

EKG shows Sinus Bradycardia with a rate of 48. Complete Blood Count shows Hemoglobin of 12 g/dL, Hematocrit of 37%, and a mean corpuscle volume of 90.7. Basic Metabolic panel was within normal limits with a Sodium of 140 mmol/L, Potassium of 3.9 mmol/L, Chloride of 105 mmol/L, a Creatinine of 0.8 mg/dL, and a BUN of 9 mg/dL. Fatigue and dizziness thought likely due to medication adverse effect; will decrease Metoprolol and monitor for improvement.

Literature Review

In the above case study, an older adult with underlying dementia on cholinesterase inhibitors and atypical antipsychotics presented with fatigue and was found to be hypotension with symptoms suggestive of orthostatic hypotension. In addition, bradycardia and antihypertensive medication use was reported. The relationship between the probable symptomatic orthostatic hypotension, diagnosis of dementia, antihypertensive use, risk of falls, and contributory role of antipsychotics will be further explored.

Definition of Orthostatic Hypotension

In 2011, an updated consensus statement endorsed by the American Autonomic Society, the European Federation of Autonomic Societies, and the American Academy of Neurology was released clarifying the definition of orthostatic hypotension given expanded understanding of the disorder (Freeman et al., 2011). The consensus statement defines orthostatic hypotension as "a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table" (Freeman et al., 2011, p. 69). Orthostatic hypotension may be symptomatic, with characteristic symptoms such as dizziness, lightheadedness, pre-syncope, or syncope, or, with more generalized symptoms such as fatigue, headache, and weakness (Freeman et al., 2011). Orthostatic hypotension may also be asymptomatic (Freeman et al., 2011). Asymptomatic orthostatic hypotension is more prevalent than symptomatic orthostatic hypotension (Benvenuto & Krakoff, 2011; Butt & Harvey, 2015). Various etiologies of orthostatic hypotension exist and are often classified into neurogenic orthostatic hypotension, those related to neurodegenerative disorders, and non-neurogenic orthostatic hypotension, of which include pharmacological and vasculature factors (Sambati, Calandra-Buonaura, Poda, Guaraldi, & Cortelli, 2014). Regardless of the

etiology, orthostatic hypotension represents a failure of the neurocardiovascular mechanisms to control blood pressure in response to gravitational stress with failure of these mechanisms leading to impaired cerebral perfusion (Freeman et al., 2011; O'Callaghan & Kenny, 2016).

Mechanisms of orthostatic regulation. Upon standing, an immediate gravitational redistribution blood volume occurs (Freeman et al., 2011). Blood volume, an estimated 500 to 700 mL, is redistributed to the lower extremities, splanchnic bed, and pulmonary circulation resulting in decreased cardiac preload and, subsequently, decreased cardiac output (Perlmuter et al., 2012). Several neurocardiovascular mechanisms are responsible for maintaining cerebral blood flow and include the baroreceptor reflex, the renin-angiotensin-aldosterone system, and cerebral autoregulation (Perlmuter et al., 2012). The brain is extremely dependent on a continuous blood supply and these mechanisms ensure the continued maintenance of adequate cerebral blood flow (Van Beek & Claassen, 2011).

The arterial baroreceptor reflex is initiated by reduced stretch within the arterial baroreceptors within the carotid sinus, intima of the aortic arch, and the ventricles of the heart as a result of decreased venous pressure, cardiac output, and, therefore, arterial blood pressure (Perlmuter et al., 2012). The baroreceptor afferent pathway terminates in the caudal area of the solitary nucleus and the paramedian nucleus of the reticular formation in the brainstem where it is relayed to the hypothalamus, cerebellum, substantia nigra, and the cerebral hemispheres (Perlmuter et al., 2012). The multisynaptic efferent baroreceptor response leads to norepinephrine release from the thoracolumbar spinal nerves stimulating alpha-adrenergic receptors causing vasoconstriction, shifting redistributed blood from the lower extremities and splanchnic bed to the central venous system, and reestablishing cardiac output (Perlmuter et al., 2012).

Cerebral autoregulation, another mechanism of orthostatic regulation, assists in maintaining stable cerebral perfusion in response to changes in the systemic blood pressure (O'Callaghan & Kenny, 2016). In response to decreased arterial blood pressure, cerebral autoregulation decreases cerebral vascular resistance through vasodilation to maintain blood flow to the sensitive cerebral tissue avoiding cerebral hypoperfusion (Perlmuter et al., 2012). Increased arterial pressure leads to vasoconstriction increasing cerebral resistance as a result of cerebral autoregulation (Perlmuter et al., 2012).

Prevalence of Orthostatic Hypotension

The prevalence of orthostatic hypotension increases with aging (Benvenuto & Krakoff, 2011). In a large (*n*= 33,346) prospective study of middle-aged adults with a mean age of 45.7, 6.2% of study participants were found to have baseline orthostatic hypotension (Fedorowski et al., 2010). In comparison, a large (*n*= 2,321) prospective study of older adults with a mean age of 65.5 years found 16.6% of the participants had baseline orthostatic hypotension (Yap, Niti, Yap, & Ng, 2008). Another large (*n*= 5,201) prospective study of adults 65 years and older demonstrated a positive association with orthostatic hypotension with adults 65-69, 70-74, 75-79, 80-84, and 85+ years of age having a 14.8%, 19.2%, 20.1%, 20.2%, and 26% prevalence of orthostatic hypotension respectively (Rutan et al., 1992).

Hypertension is also positively associated with orthostatic hypotension. In a large (*n*= 722) prospective population based study of adults 70 years and older, orthostatic hypotension was highest in participants with a blood pressure of greater than or equal to 140/90 mmHg (Gangavati et al., 2011). In these hypertensive participants, 19% had systolic orthostatic hypotension at one minute compared to 2% in those without hypertension ($p \leq .001$) (Gangavati et al., 2011).

Alzheimer's disease is also positively correlated with orthostatic hypotension irrespective of advanced age. In a cross-sectional study of 235 individuals with Alzheimer's disease with a mean age of 76 years of age, 42% of the participants had orthostatic hypotension (Andersson, Hansson, Minthon, Ballard, & Londos, 2008). This is compared to 62 individuals without cognitive impairment with a mean age of 73 years of age whom only 13% had orthostatic hypotension (Andersson et al., 2008). In another cross-sectional study by Sonnesyn et al. (2009) 128 participants with Alzheimer's disease with a mean age of 75.6 years found 41% had orthostatic hypotension present compared to 14% of the control participants with a mean age of 75.5 years. The strong association of Alzheimer's disease with orthostatic hypotension is clear and it is evident the association cannot be accounted for solely based on age.

Orthostatic Hypotension in the Older Adults

Several physiological changes of aging may lead to the development of orthostatic hypotension. Increased arterial stiffness, often as a result of age-related decreases in arterial compliance, has been demonstrated to be independently associated with orthostatic hypotension and is related to decreased baroreceptor sensitivity and inability of the cerebral vasculature to effectively vasodilate limiting cerebral autoregulation in response to decreased arterial blood pressure (Mattace-Raso et al., 2006; Perlmuter et al., 2012). Therefore, cerebral autoregulation is impaired with abrupt changes in systemic arterial blood pressure leading to a substantial change in cerebral blood flow (O'Callaghan & Kenny, 2016). Impaired alpha-adrenergic vasoconstriction, particularly in the splanchnic system that is responsible for approximately one-third of blood volume redistribution during standing, has been demonstrated with advanced age (O'Callaghan & Kenny, 2016). Impaired cardiac diastolic filling and subsequent reduced stroke volume decreases venous return, particularly with orthostatic stress, which is further exacerbated

by a diminished heart rate response to these orthostatic stresses in those of advanced age (O'Callaghan & Kenny, 2016; Perlmuter et al., 2012).

Pathogenesis of Orthostatic Hypotension in Alzheimer's Disease

While the increased prevalence of orthostatic hypotension in Alzheimer's disease has been established, the underlying etiology remains controversial. Several studies have highlighted possible links to the increased prevalence of orthostatic hypotension in individuals with Alzheimer's disease.

A complicated relationship with blood pressure and Alzheimer's disease development has been shown in studies. Multiple longitudinal prospective studies have shown an increased risk of Alzheimer's disease in later life with hypertension in midlife (O'Callaghan & Kenny, 2016; Qiu, von Strauss, Winblad, & Fratiglioni, 2004). Clinical trials have not demonstrated a relationship with antihypertensive medications and dementia risk (Butt & Harvey, 2015). In advanced age, however, the inverse relationship occurs with hypertension having a protective effect and relative hypotension increasing the risk of cognitive impairment. In a study of community living adults 55 years and older with a mean age of 65.5 years (n= 2,321), individuals with a blood pressure of less than 120/70 mmHg and with orthostatic hypotension were found to have a significantly increased risk of cognitive impairment at baseline (OR= 4.1) (Yap et al., 2008). The study did not find an association with orthostatic hypotension and the risk of developing cognitive decline over a two-year follow-up period (Yap et al., 2008). In a study by Qiu et al. (2004) of community living adults 75 years and older without dementia (n= 947) were followed for a period six years assessing the association with blood pressure and risk of dementia according to the DSM-III revised edition. The study demonstrated systolic blood pressure significantly decreased in the three-year period prior to the diagnosis of dementia; as a

continuous variable, each 10 mmHg decrease in systolic blood pressure adjusted the relative risk of Alzheimer's disease to 1.09 (Qiu et al., 2004). For participants with a baseline blood pressure of less than 160 mmHg, a systolic pressure decline of 15 mmHg or more occurring 3 to 6 years prior to the diagnosis of cognitive impairment was associated with a relative risk of 3.1 for Alzheimer's disease (Qiu et al., 2004).

For those individuals with Alzheimer's disease, greater blood pressure reduction with antihypertensive medication has been shown to lead to a more rapid progression of cognitive decline in Alzheimer's disease. In a study by (Mossello et al., 2015) of cognitively impaired adults, 68% with dementia, with the mean age of 79 years, 172 participants were followed for a median of 9 months with Mini-Mental State Examination (MMSE) at baseline and follow-up in addition to ambulatory blood pressure monitoring. Of the participants, 69.8% were receiving antihypertensive medications (Mossello et al., 2015). Participants taking antihypertensive medications with a daytime systolic blood pressure less than or equal to 128 mmHg showed the greatest change in the MMSE score from baseline compared to baseline than participants with a daytime systolic blood pressure of greater than 128 mmHg (Mossello et al., 2015).

In another study (n= 40) participants with a clinical diagnosis of Alzheimer's disease showed a reduced 30:15 ratio, a measure of baroreceptor functioning to orthostatic stress with the ratio to the R-R interval at the 30th heartbeat and at 15th heartbeat upon standing, compared to age matched controls (Idiaquez, Sandoval, & Seguel, 2002). Among the participants with Alzheimer's disease, the 30:15 ratio correlated with an increased impairment in psychometric testing of self-care capabilities, apathy, delusions, and aberrant motor behavior (Idiaquez et al., 2002). While an association with orthostatic hypotension and increased impairment in psychometric testing in participants with Alzheimer's disease was not found, it does suggest

neurocardiovascular instability and progression of cognitive decline may be linked (Idiaquez et al., 2002).

Orthostatic changes have been shown to lead to greater reductions in cerebral cortical tissue perfusion compared to the systolic blood pressure decline in individuals with Alzheimer's disease. In a study by van Beek, Sijbesma, Jansen, Rikkert, and Claassen (2010), 21 participants with Alzheimer's disease and 20 age-matched controls had blood pressure, frontal cortical oxygenation using near-infrared-spectroscopy, and cerebral blood flow velocity in the middle cerebral artery using transcranial Doppler ultrasonography measured in response to a postural change. While, unexpectedly, postural changes in blood pressure for the Alzheimer's disease participants were more modest than the controls, participants with Alzheimer's disease had larger declines in the frontal cortical concentration of total hemoglobin (van Beek et al., 2010). In addition, participants with Alzheimer's disease also had a 57% larger decline in oxygenated hemoglobin compared to the controls (van Beek et al., 2010). Therefore, for individuals with Alzheimer's disease, smaller declines in systemic blood pressure with postural changes lead to a dramatic decline in frontal cortical concentration of total hemoglobin, especially oxygenated hemoglobin (van Beek et al., 2010). A lower supply of oxygen in the brain tissue is found during hypotensive periods in individuals with Alzheimer's disease compared individuals without Alzheimer's disease of the same age (van Beek et al., 2010).

Cholinergic-vascular hypothesis. The cholinergic-vascular hypothesis is based on the property of the cholinergic neurons of the brain to produce vasodilation augmenting cerebral blood flow (Claassen & Jansen, 2006). Alzheimer's disease has been associated with a severe loss of cholinergic innervation within brain with diminished cerebral blood flow (Van Beek & Claassen, 2011). Cholinesterase inhibitors which, reduce acetylcholine breakdown within the

synapse, partially correcting the cholinergic deficit (Claassen & Jansen, 2006). Unfortunately, cholinesterase inhibitors have been shown to have limited and unpredictable benefits for individuals with Alzheimer's disease (Claassen & Jansen, 2006). Cholinesterase inhibitor treatment effects are not specific to Alzheimer's disease with similar outcomes found in individuals with other forms of cognitive impairment such as vascular dementia, dementia with Parkinson's disease, and dementia with Lewy bodies; individuals without cognitive impairment have even shown benefits in attention, reaction time, and cognitive performance (Claassen & Jansen, 2006). Scopolamine, an anticholinergic medication that binds to muscarinic receptors, has, inversely, been shown to reduce frontal cerebral perfusion in young participants (Claassen & Jansen, 2006). It is thought these benefits demonstrated from cholinesterase inhibitors are possibly due to an improvement in cerebral blood flow (Claassen & Jansen, 2006).

The basal forebrain is the major source of cholinergic neurons within the brain with these cholinergic neurons having projections to cerebral blood vessels (Claassen & Jansen, 2006). Acetylcholine, the neurotransmitter of the cholinergic neurons primarily binds to muscarinic receptors (Claassen & Jansen, 2006). Muscarinic receptors have been identified in perivascular astrocytes, smooth muscle cells, and endothelial cells in cortical arterioles (Claassen & Jansen, 2006). Stimulation of the nucleus basalis of Meynert, a group of neurons of the basal forebrain, in rats showed a significant increase in cerebral blood flow to cortical areas of the brain (Claassen & Jansen, 2006; Van Beek & Claassen, 2011). Inversely, complete destruction of the nucleus basalis of Meynert by a cholinergic immunologic toxin resulted in a globally decreased cerebral blood flow; the posterior parietal and temporal regions were most severely affected regions of the brain (Claassen & Jansen, 2006). This distribution of hypoperfusion corresponds to the regions of the brain most prominently affected by Alzheimer's disease (Claassen &

Jansen, 2006). Loss of cholinergic innervation in cortical arterioles in brains of individuals with Alzheimer's disease, particularly within the temporal lobe, is seen when compared to age-matched controls (Claassen & Jansen, 2006). This vascular cholinergic deficit causes regional cerebral hypoperfusion contributing to the neurodegeneration and cognitive decline seen in Alzheimer's disease (Claassen & Jansen, 2006). Poor brain tissue oxygenation and impaired mechanisms to respond to hypotensive changes of orthostatic stress with cerebral vasodilation results in individuals with Alzheimer's disease being particularly vulnerable to these stresses.

The unpredictable effect of cholinesterase inhibitors may be explained by the cholinergic vascular hypothesis. Cholinergic augmentation of cerebral blood flow can only occur if the cerebral vasculature is able to respond with vasodilation; microvascular disease and endothelial dysfunction limit cholinergic vasodilation (Claassen & Jansen, 2006; Van Beek & Claassen, 2011). Individuals with Alzheimer's disease who have responded to cholinesterase inhibitors have shown an improvement or stabilization of cerebral blood flow while non-responders had a continued progressive decline of cerebral blood flow (Van Beek & Claassen, 2011).

Falls and Orthostatic Hypotension

Falls, a leading cause of disability in the older population, and orthostatic hypotension is often thought to have a positive direct association though several extensive literature reviews have not clearly shown such relationship exists (Gangavati et al., 2011; Shaw, Loughin, Robinovitch, & Claydon, 2015). Falls are a significant cause of injury, loss of confidence, and decline in functional, social, and physical activities, in addition to institutionalization in older people (Allan, Ballard, Rowan, & Kenny, 2009; Stel, Smit, Pluijm, & Lips, 2004). If an association with orthostatic hypotension and falls does exist, its association is strongest for symptomatic as opposed to asymptomatic orthostatic hypotension.

In a small study conducted by Shaw et al. (2015) of older adults in a long-term care facility, participants *(n*= 59) underwent orthostatic stress testing and results were compared between those who had fallen one or more times in the previous year compared to those who had not fallen in the previous year; the study was not specific to individuals with Alzheimer's disease though no statistically significance difference in cognitive performance testing or presence of Alzheimer's disease between the two groups was found. Differences in orthostatic stress testing between the two groups showed cerebral blood flow declines were greater among those who had fallen one or more times in the previous year compared to those who had not (Shaw et al., 2015). This study highlights the importance of cerebral blood flow as an important variable to increasing fall risk. Reductions in cerebral blood flow, either as a result of impaired cerebral autoregulation or orthostatic hypotension, may cause syncope leading loss of postural tone precipitating a fall (Shaw et al., 2015). Cognitive functioning may also be negatively affected with decreases in cerebral blood flow indirectly leading to a fall (Shaw et al., 2015).

In a systematic review of nine studies conducted by Angelousi et al. (2014) reviewing the association between orthostatic hypotension and falls, six studies did not find an association with increased fall risk and orthostatic hypotension. These studies that did not find an association between these variables were not specific to individuals with Alzheimer's disease though the studied populations were older adults (Angelousi et al., 2014).

In another prospective study by Gangavati et al. (2011), community living older adults had baseline orthostatic testing completed and then were followed for one year with monthly fall data completed. The study was not exclusive to individuals with Alzheimer's disease or cognitive impairment and did exclude individuals with moderate to severe cognitive impairment

as defined by a MMSE of less than 18 (Gangavati et al., 2011). The study did not find orthostatic hypotension was, by itself, associated with falls (Gangavati et al., 2011).

A longitudinal cohort study conducted by Allan et al. (2009) was specific to individuals with dementia (*n*= 179) which evaluated the prevalence of falls during a 12 month follow-up period. Baseline measurements of the cohorts included orthostatic stress testing and evaluation of the presence of symptoms of orthostatic hypotension with testing (Allan et al., 2009). Individuals with Alzheimer's disease experienced 1.95 more falls than the age-matched controls (Allan et al., 2009). While the presence or absence of orthostatic hypotension was not found to be predictive of falls, symptomatic orthostatic hypotension was predictive (Allan et al., 2009). Individuals with Alzheimer's disease have a higher incidence of falls with the presence of symptomatic orthostatic hypotension in those individuals being predictive of falling.

Atypical Antipsychotics and Orthostatic Hypotension

Atypical antipsychotics, such as Quetiapine, is often used to assist in the management of agitation, aggressiveness, and psychosis of Alzheimer's disease which begin to appear in the mild to moderate stages of the disease becoming increasingly severe with the progression of the disease (Onor, Saina, & Aguglia, 2006). Unfortunately, these atypical antipsychotics are associated with orthostatic hypotension (Perlmuter et al., 2012). In a study conducted by Onor et al. (2006), of 41 patients with dementia, 20 of which had Alzheimer's disease, Quetiapine was effective in reducing behavioral symptoms, hallucinations, and sleep disturbances according to psychometric testing after 12 weeks of therapy (Onor et al., 2006). In general, Quetiapine was tolerated among the participants with the exception of orthostatic hypotension (Onor et al., 2006). Of the participants, 12.2% discontinued treatment due to syncope and persistent orthostatic hypotension (Onor et al., 2006). Another 4.8% of the participants in the study

required a dose reduction and slower dose titration due to orthostatic hypotension (Onor et al., 2006). While atypical antipsychotics have shown to be beneficial for the behavioral and psychological symptoms of dementia, the adverse effect of orthostatic hypotension must be considered.

Learning Points

- While orthostatic hypotension is more prevalent with age, it is particularly more prevalent in individuals with Alzheimer's disease regardless of age.
- Alzheimer's disease development is associated with a significant decrease in systolic blood pressure in the three-year period prior to the diagnosis of dementia and, for those with established Alzheimer's disease, further lowering of the blood pressure with antihypertensive medications may hasten the disease progression.
- The acetylcholine deficit present in Alzheimer's disease decreases cerebral blood flow due to the role of acetylcholine in vasodilation of the cerebral vasculature.
- For individuals with Alzheimer's disease, smaller declines in systemic blood pressure with orthostatic stress results in large declines in the supply of oxygenated hemoglobin.
- The relationship with orthostatic hypotension and falls is unclear, but evidence suggests that for individuals with Alzheimer's disease presence of symptomatic orthostatic hypotension is predictive of falls due to decreased cerebral blood flow.

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