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The Effects of Hyperhomocysteinemia on Hypertension in Adults

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PERMISSION

Title: The Effects of Hyperhomocysteinemia on Hypertension in Adults

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Abstract

Although research suggests that hyperhomocysteinemia (Hhcy) influences the development of cardiovascular disease, the hypothesis that Hhcy specifically causes hypertension remains a relatively mysterious subject. Despite the suggestion that Hhcy is linked to hypertension, there currently are no guidelines on hypertension treatment related to serum homocysteine concentration.

The following case discusses a 67-year-old Caucasian female with recently diagnosed hypertension. She presents to her primary care clinic for a three-week follow-up exam after beginning an antihypertensive regimen in accord with her diagnosis of essential hypertension. Her blood pressure remains uncontrolled, despite pharmacologic intervention.

Hypertension is an illness seen commonly in primary care. Hypertension that is poorly controlled increases the risk of cardiovascular complications such as myocardial infarction, stroke, and heart failure; therefore, it is necessary to be knowledgeable about the causes and treatments of hypertension.

Background

A 67-year-old Caucasian female presented to the clinic for a three-week follow-up after a recent diagnosis of essential hypertension, for which she was started on antihypertensive therapy. She reports a history of smoking, but has no additional past medical history. However, her family history is significant for coronary artery disease and diabetes. Despite pharmacologic antihypertensive therapy in conjunction with an active lifestyle, her blood pressure remains elevated.

Hypertension has long been recognized as a modifiable risk factor for heart disease. The etiology of hypertension is not yet fully understood, but remains important as its prevalence continues to grow worldwide (Wang et al, 2014). For decades, there have been studies looking at the relationship between homocysteine levels and the risk of cardiovascular disease. More recently, elevated homocysteine, or hyperhomocysteinemia (Hhcy), has been viewed as a risk factor for elevated blood pressure in adults. It is necessary to consider the relationship between homocysteine and blood pressure as studies have proven that interventions (such as supplementation of folic acid) can reduce serum levels of homocysteine (Anderson, Ha Jee, Charleston, Narrett, & Appel, 2010). If, in fact, Hhcy can be linked to hypertension, it would be prudent for providers to know how to diagnose and treat this condition.

Case Report

History

A 67-year-old Caucasian female presents to the clinic for a follow-up exam after a recent diagnosis of essential hypertension. She was started on antihypertensive therapy three weeks ago, which consisted of Lisinopril 20 mg once daily. She has been monitoring her blood pressure daily, with an average systolic blood pressure reading in the 150’s.

At this visit, she is feeling well except for a persistent dry cough, which has been present for the past three weeks. When asked about associated symptoms, she reports no fever, chills, wheezing, shortness of breath, or upper respiratory symptoms. She reports no increased anxiety or stress, and states “other than this cough, nothing has seemed out of the ordinary”. She does not mention that her cough is worse with exertion, nor does it interfere with daily activities. Other pertinent negatives include no chest pain, palpitations, dizziness, or syncope.

Other than newly diagnosed hypertension, she denies comorbidities including dyslipidemia or diabetes. She gives a brief overview of her family history, which is concerning as both parents have undergone coronary artery bypass graft, indicating significant coronary artery disease. After mentioning this, she explains that at age 53 she had an episode of chest pain, which eventually led to an angiogram. Regarding the angiogram, she recalls “the cardiologist told me my arteries were clean at that time”. Her family history also includes a brother with diabetes.

She is currently retired and lives an active lifestyle. She loves to swim, often 6 miles at a time, and participates in a water aerobics class at a nearby gym, three to four days per week. She has a 30 pack-year history of smoking, having quit more than 10 years ago. She does not consume alcohol and has never used any other form of drugs.

Her current medications include Lisinopril 20 mg once daily, in addition to a daily multivitamin. She uses no other over-the-counter or herbal medications, and denies any drug allergies.

Physical Exam, Diagnosis, and Treatment Plan

The following vital signs are obtained at this visit: Blood pressure 160/98, heart rate 80, respiratory rate 20, and temperature 98.6 F. During her exam, she is pleasant and engaged in conversation, showing no signs of distress.

The physical exam at this visit reveals clear conjunctiva without drainage, and pupils that are equal, round, and reactive to light and accommodation, bilaterally. Her funduscopic exam is unremarkable, bilaterally. No nasal mucosa inflammation or discharge is noted, which aids in ruling out an upper respiratory cause of her cough. Her oropharynx is pink, moist, and free of lesions or exudate. Her neck is supple, non-tender, and without masses. Her cardiovascular exam reveals a regular heart rate and rhythm, with no evidence of a murmur or adventitious heart sounds. Trace peripheral edema is noted to the lower extremities. Her breathing is regular and non-labored during the exam. Lung sounds are clear throughout all lung fields, with no wheezing or crackles noted. Her abdominal assessment is negative. She is alert and oriented to person, place, and time. Her skin is warm and dry to touch with no evidence of rash, bruising, or wounds.

No laboratory testing or diagnostics were obtained at this visit. Given the patient's history and physical exam which indicate no signs of an infectious process, it is likely that her persistent dry cough is related to the ACE inhibitor started three weeks prior. After determining that her cough is likely an adverse effect of an ACE inhibitor, Lisinopril is discontinued. She is informed that her blood pressure should be less than 150/90, per JNC-8 guidelines on the treatment of hypertension. As such, she will need to start an antihypertensive from another drug class. In further reference to the JNC-8 guidelines on management of high blood pressure, Hydrochlorothiazide 25 mg once daily is prescribed (James et al., 2014). The patient is given information on this new prescription and questions are answered. She is encouraged to continue

water aerobics three to four days a week, and may monitor her blood pressure at home as desired. She is recommended to follow-up in four weeks for a recheck of her blood pressure, as well as lab work, due to the potential for Hydrochlorothiazide to alter electrolytes and renal function. Additionally, a fasting lipid panel will be ordered at her follow-up visit due to a significant family history of coronary artery disease, as well as a personal history of smoking. The patient is instructed to follow-up sooner than four weeks if her cough does not improve, or if she develops other concerning symptoms. She agrees with this treatment plan, and with follow-up related to her diagnosis of hypertension.

As demonstrated in the previously discussed case report, treatment for hypertension is not always straightforward. Many factors play into the cause of hypertension, factors which may vary among individuals and alter treatment outcomes. It is important for providers to understand what factors influence hypertension, as having that understanding will allow for the most appropriate treatment to be given. In the past century, homocysteine was discovered to be a contributing factor in cardiovascular disease. In more recent years, research has also looked at how increased levels of homocysteine may directly affect blood pressure (Li et al., 2016).

Literature Review

Hyperhomocysteinemia has been investigated by researchers as a possible cause of hypertension in adults. To better understand how Hhcy may affect the cardiovascular system, it is essential to first understand what homocysteine is. Homocysteine is an amino acid which contains a sulphur compound formed via the biosynthesis of cysteine and methionine (also amino acids). It is largely formed via the replacement of a molecule from the amino acid methionine. Methionine is found to be plentiful in animal proteins (Ganguly & Alam, 2015). The most common causes of Hhcy are due to genetic or environmental reasons. For example, a

deficiency in vitamin B12 or folic acid can inhibit the ability of homocysteine to be broken down, rendering increased intracellular concentrations. The sulphur component found in homocysteine can cause oxidative damage, or the inhibition of antioxidant properties, within the tissues so the body cannot counteract the harmful effects of free radicals. Therefore, Hhcy can cause a hypercoagulable state and rapid proliferation (i.e. reproduction) of smooth muscle cells. Rapid proliferation of smooth muscle cells in the vessel endothelium may cause arterial stiffness and thus hypertension (Korzeniowska, Cieslewicz, Chmara, & Jablecka, 2015).

Hyperhomocysteinemia is defined as a serum homocysteine level greater than 15 umol/L. Most healthy persons have a homocysteine level between 5.0 and 15.0 umol/L, depending on the method being used to interpret this value. A homocysteine level between 16 and 30 umol/L is defined as moderate, a level between 31 and 100 is reported as intermediate, and severe Hhcy is considered any value above 100 umol/L (Ganguly, 2015). As one source reports, the normal range for serum homocysteine concentration tends to increase with age. Consequently, this places adults at an increasing risk of Hhcy as they age (Korzeniowska et al., 2015). In caring for an aging adult population, the ability to determine the presence of Hhcy becomes important, as this may affect blood pressure.

There are many reasons to consider the relationship between Hhcy and hypertension, with perhaps the most important reason being a reduction in the risk of cardiovascular morbidity and mortality (Lionakis, Mendrinos, Sanidas, Favatas, & Georgopoulou, 2012). Making the connection between Hhcy and blood pressure will aid in the development of hypertension treatment plans to reduce serum homocysteine levels.

The review of literature surrounding this topic led to several types of studies that have been performed in multiple countries, with most studies being investigated in China. Although it

is not recent, the Framingham Heart Study, originally published in 2003, was the first study to look at whether increased serum homocysteine levels caused hypertension. The relevance of this source is proven through its frequent citation within more recent studies, and so, should be discussed within this case report. At the time that this prospective longitudinal study was completed, several cross-sectional studies had observed an increased risk of cardiovascular disease in the presence of Hhcy, but none had looked at whether it was the cause of high blood pressure (Sundstrom et al., 2003).

The goal of the Framingham Heart study, was to investigate the progression of blood pressure in relation to serum homocysteine, over a four-year follow-up. Homocysteine levels were analyzed based on the following criteria: as sex-based quartiles; as Hhcy (which was considered > 14 umol/L); and as models with multiple variables known to influence blood pressure (i.e. diabetes mellitus, obesity, smoking, creatinine level, and blood pressure category). At the four-year follow-up exam, 360 of the 2,104 participants had developed hypertension. Rates were similar among genders, and those with homocysteine levels above 14 umol/L had a higher incidence of hypertension. However, in the models that had been adjusted for age and sex, and in the models with multiple variables, the correlation between homocysteine level and blood pressure elevation was not statistically significant. And so, the Framingham Heart Study concludes that Hhcy is likely a concomitant finding, rather than a causative factor in the development of hypertension (Sundstrom et al., 2003).

Per Ganguly and Alam (2015) the role of homocysteine in the control of blood pressure deserves some attention, as blood pressure may facilitate the toxic effects of homocysteine on the cardiovascular system. Experimental and animal studies have shown a link between homocysteine and hypertension when an increase in blood pressure was seen after inducing

hyperhomocysteinemia. The resulting increase in blood pressure may be due to changes in vascular endothelial integrity. Cell culture studies performed in artificial environments have shown that with the administration of homocysteine, there was induction of oxidative stress to the vascular endothelium and decreased availability of nitric oxide. Without the vasodilatory effect of nitric oxide, the endothelium was less able to react to vasoconstriction, which increased blood pressure. This study also reports that impairments in vascular endothelium vasodilation have been noted in humans with acute or chronic Hhcy, suggesting that Hhcy does in fact contribute to hypertension (Ganguly & Alam, 2015).

In further review of the literature, similar findings were discussed in the European Journal of Physiology, regarding the hypothesis of vascular endothelial injury due to oxidative stress. Peripheral circulation is, in part, controlled by both vasodilatory and vasoconstricting factors such as nitric oxide and oxidative stress, respectively. Hhcy influences peripheral blood flow primarily by impairing the actions of such vasodilators. A confounding effect is that Hhcy contributes to oxidative stress, which works against nitric oxide, so it is not able to generate its full potential of vasodilation. In one study, adults were given oral methionine which increased their homocysteine level and resulted in a reduction in flow-mediated vasodilation of the endothelium within the brachial artery. The reduction in dilation was significant, compared to adults with low levels of homocysteine. Thus, signifying that Hhcy is an independent risk factor for decreased function of arterial endothelium, and so a risk for hypertension. Two additional studies have found that oral methionine increases homocysteine levels, and impairs the action of endothelial dilatation in healthy adults. The findings of this study indicate that there is a positive correlation between Hhcy and alteration of vessel endothelium, which may cause arterial stiffness and hypertension (Toda & Okamura, 2016).

Korzeniowska et al. (2015) discuss, as many other studies have, the effects of endothelial dysfunction in the presence of elevated homocysteine levels. With that background, the authors of this study looked at the relation of homocysteine levels, to newly diagnosed essential hypertension in adults. Age and smoking were considered associated factors in this study. The patients who fell into the essential hypertension category per JNC VII criteria, had shown higher serum homocysteine (mean 15.23 umol/L) compared to the control group (mean 9.71 umol/L). Among participants, 28 percent had a homocysteine level of 15 umol/L or greater. Also, in those with hypertension who were smokers, homocysteine levels were higher than non-smokers. Age was the only factor shown to correlate with homocysteine level in healthy participants without hypertension (Korzeniowska et al., 2015).

A prospective Kailuan study, looked at homocysteine levels and the progression of blood pressure among a community cohort of 2427 men and women, over 2 years. Within the male cohort, the incidence of hypertension was most significant at a lower homocysteine level, and showed reduced progression of hypertension as homocysteine levels increased. Within the female cohort, there was not a significant correlation found between homocysteine level and blood pressure. This 2-year longitudinal study concluded that rather than Hhcy increasing the risk of hypertension, lower homocysteine levels might be a risk factor for the occurrence of high blood pressure (Wang et al., 2014).

In Northeast rural China, a large cross-sectional study looked at the independent association of Hhcy and hypertension among 7,130 people aged 35 years and older within the general population. Upon completion, a trend was seen between increased levels of homocysteine and the incidence of hypertension. After adjusting for patient variables such as age, body mass index, smoking, family history of hypertension, and comorbidities, the findings

of several logistic regression analyses demonstrated a significant association of Hhcy and high blood pressure among males, but this association was not seen in females. In addition, the prevalence of Hhcy was much higher in males than females, with a mean homocysteine level in men of 20.99 umol/L and 14.19 umol/L in women. Interestingly, the mean level of homocysteine in males within this study is significantly higher than the mean typically reported among studies completed in other countries, suggesting that future research should investigate environmental or cultural factors associated with homocysteine levels. The results of this study concluded that there was a positive correlation between Hhcy and the prevalence of hypertension in males, and that homocysteine levels tend to be higher in males than females (Li et al., 2016).

It has been noted within multiple studies, that folate intake may reduce blood pressure as it increases the activity of nitric oxide, which leads to vasodilation of vessels and reduced serum homocysteine levels (Anderson et al., 2010; Toda & Okamura, 2016; Van Dijk et al., 2015; Xun et al., 2012). One study looked at how the ingestion of folate affected the incidence of hypertension among young African American and Caucasian adults, over a 20-year follow-up. This follow-up study used data obtained from 6 follow-ups of the Coronary Artery Risk Development in Young Adults (CARDIA) study, which examined the progression of cardiovascular disease based on risk factors. While this study was directly focused on the link between hypertension and folate intake, it also assessed the relation between folate and homocysteine levels, looking for a potential mechanism as to why the former link exists. Of importance, were the examinations of how serum levels of folate related to homocysteine levels, how homocysteine concentration related to blood pressure, and the relation of serum homocysteine to newly diagnosed hypertension. The study found an inverse link between the level of folate in the blood and the level of homocysteine. Participants with higher levels of

folate had lower serum concentrations of homocysteine, and a lower incidence of hypertension. Furthermore, as homocysteine levels increased by 5 umol/L, systolic blood pressure increased by 0.63 mmHg and diastolic blood pressure increased by 0.55 mmHg. Despite being unable to prove whether folate directly reduced serum homocysteine concentrations, the study did find that higher rates of hypertension were noted among those with higher concentrations of homocysteine (Xun et al., 2012).

Finally, although multiple studies make note of the hypothesis that Hhcy may contribute to hypertension, studies have failed to prove a strong predictable causation between Hhcy and hypertension. The literature available on this topic is insufficient, especially works within the past decade, indicating that further investigation is needed. It was found that Hhcy has been linked to an increased risk of atherosclerosis, heart failure, and stroke. The correlation between Hhcy and the previously mentioned cardiovascular diseases, provides plausible reason to continue researching the relationship between Hhcy and hypertension.

Learning points

- Hhcy has been proven in some instances to cause harm to vascular endothelial integrity via oxidative stress, owing to arterial stiffness which may contribute to hypertension.
- The relationship between Hhcy and hypertension in adults are conflicting among studies, thus a definitive correlation cannot be made between the two.
- There is a lack of high level evidence studies surrounding the topic of Hhcy and its effect on hypertension in adults.
- It is suggested that future studies include monitoring of serum nitric oxide levels in participants, as this may give further insight to the relationship between Hhcy and hypertension.

Resources

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