Chiropractic Management of Chronic Hypertension: Comprehensive Differential Diagnosis

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Given the high clinical importance and prevalence of hypertension (HTN) in general clinical practice, Doctors of Chiropractic (DC) should remain aware of its differential diagnosis so that proper patient management can be implemented and so that the underlying causative factors can be addressed when possible. Listed below are many of the more common primary causes of hypertension with a brief sketch of their classic clinical characteristics, including physical examination and laboratory findings. This information is excerpted and updated from the recently published guidelines “Chiropractic Management of Chronic Hypertension” published by Vasquez.1

Major Differential Diagnoses of Chronic Hypertension:

Characteristics of secondary hypertension include therapeutic recalcitrance, onset at an early age (< 30y) or at a more advanced age (>50y), and the typical associated features of the causative disorder, such as hypokalemia with hyperaldosteronism, depression or musculoskeletal pain with hypovitaminosis D, and cold intolerance, bradycardia, and delayed Achilles reflex return with hypothyroidism.

• Aortic coarctation: Classic presentation includes upper extremity hypertension with lower extremity hypotension/hypoperfusion/claudication in a child or young adult; secondary activation of the renin-angiotensin system due to renal hypoperfusion exacerbates the HTN and complicates this focal anatomic disorder by adding a systemic neurohormonal component. Aortic coarctation is diagnosed by imaging the aorta with computed tomography (CT), magnetic resonance imaging/angiography (MRI/MRA), or echocardiogram (echo) or transthoracic ultrasound (US). Treatment includes antihypertensive interventions (reviewed in the section on Therapeutic Considerations) to manage the hypertension until surgery corrects the coarctation.

• Cocaine use: Cocaine use can cause acute and chronic elevations in blood pressure. Drug cessation is the key to treatment; urine drug testing is appropriate for patients suspected of undisclosed drug use or noncompliance with cessation. In hospital practice, patients presenting with hypertensive disorders, chest pain, and other cardiovascular syndromes are routinely tested for acute (serum drug screen) and chronic (urine drug screen) drug exposure; an impressive number of these tests come back positive even among patients who swear to have never used or not recently used recreational drugs.

• Cushing’s disease/syndrome: Excess glucocorticoids whether endogenous or exogenous promote sodium retention directly via their mineralocorticoid effect and by causing hyperinsulinemia via induction of peripheral insulin resistance; both of these pathophysiologic processes contribute to HTN. Useful tests include measurements of serum adrenocorticotropic hormone (ACTH), urinary/salivary cortisol in addition to looking for the clinical characteristics of moon facies, striae, sarcopenia, and abdominal obesity. Treatment is withdrawal of exogenous steroids (if possible) for iatrogenic Cushing’s syndrome, or surgical removal of the ACTH-producing pituitary corticotroph adenoma (classically) in cases of endogenous Cushing’s disease. An additional type of Cushing’s syndrome can result from ectopic ACTH production from tumors such as small cell carcinoma of the lung or a carcinoid tumor.

• Estrogen, oral contraceptives: As a group of various hormones with divergent effects, estrogens generally tend to promote sodium and water retention, which promotes volume overload and the development of HTN. For women with “estrogen dominance” due to excess endogenous production or exogenous administration of estrogens, supplementation with pyridoxine 50-250 mg/d (nearly always co-administered with magnesium 600-1,200 mg/d or to bowel tolerance) and/or natural progesterone (rather than a synthetic progestin, since many of these preparations have inherent glucocorticoid/mineralocorticoid activity) can frequently offset the HTN-inducing effects of estrogens. Clinicians desiring a more comprehensive anti-estrogen protocol within a context of practical hormone optimization (“orthoendocrinology”) may find helpful the review in chapter 4 of Integrative Rheumatology.2

• Ethanol: Excess ethanol consumption raises blood pressure and makes HTN more difficult to treat. Many patients fail to accurately disclose the extent and duration of their alcohol consumption.

• Hypercalcemia: Easily diagnosed by routine labor-

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Foci of neurogenic hypertension can reside in the central nervous system (CNS) or peripheral nervous system (PNS). In this text, “central neurogenic hypertension” is used to describe hypertensive states induced by irritation of the central nervous system, in particular at the level of the brainstem (i.e., medulla oblongata in general and the root entry zones [REZ] of cranial nerves 9 and 10 as well as the nucleus tract solitarius [NTS] in particular) as will be reviewed in a following section on surgical interventions for the treatment of medullary neurovascular compression. The first use of the term central neurogenic hypertension of which the current author is aware was published by Reis in a 1981 review, mostly of animal research; in this review, Reis included the hypothesis that irritation of the CNS by either mechanical or neurochemical means could serve as a predisposition or antecedent to the manifest development of clinical HTN. The diagnosis of central neurogenic hypertension is generally based upon 1) MRI/MRA or CT findings of neurovascular compression of the left medulla oblongata in conjunction with 2) reduction in blood pressure following decompressive intervention. “Peripheral neurogenic hypertension” as an entity is more theoretical, less studied, and might be exemplified by irritation of spinal nerve roots and sympathetic ganglia as discussed primarily in the chiropractic and osteopathic literature. Functional compromise in general and facilitation in particular of the nerve roots and sympathetic ganglia as a potential cause of or contributor to chronic HTN supports the rationale for the use of spinal manipulation and manual medicine for the treatment of HTN and other nonmusculoskeletal disorders. Peripheral neurogenic hypertension may be diagnosed based on clinical/electrographic/vasodynamic evidence of functional PNS compromise/facilitation/irritation and alleviation of HTN following appropriate regional intervention such as manual manipulative treatment of the spine and adjacent neuromusculoskeletal structures applied to effect restoration of proper nervous system function and balance. Central and peripheral types of neurogenic HTN will be discussed in more detail later in this chapter within the context of their surgical and manipulative treatments, respectively.

Nonsteroidal anti-inflammatory drugs (NSAIDs): NSAIDs in general and COX-2 inhibitors (coxibs) in particular reduce endogenous production of vasodilating prostacyclin and thus cause pharmacologic/iatrogenic renal artery constriction, which leads to varying degrees of HTN via activation of the renin-angiotensin system. This explains, in part, the in-
increased cardiovascular mortality due to overutilization of coxibs such as rofecoxib/Vioxx, withdrawn from the US market in 2005 by the US FDA due to its causal role in increasing cardiovascular deaths.\textsuperscript{14} Evidence of increased cardiovascular morbidity and mortality secondary to coxib use was widely publicized for several years before rofecoxib/Vioxx and a similar drug valdecoxbi/Bextra were belatedly withdrawn from the consumer market\textsuperscript{15,16}; the multiple failures involved in this politicopharmaceutical phenomenon include 1) failure of Merck to act on data showing that it’s popular and profitable new drug was harming and killing an unacceptable proportion of patients who took it, 2) failure of the US FDA to regulate the pharmaceutical Industry, 3) failure of the medical profession as a whole to police itself and call for a ban on the use of this drug before either Merck or the FDA took action. See Eric Topol’s “Failing the public health—rofecoxib, Merck, and the FDA” published in the October 21, 2004 issue of New England Journal of Medicine for authoritative discussion.

- **Pheochromocytoma:** Exceedingly rare in contrast to the frequency with which it is covered in textbooks and licensing board exams, pheochromocytoma’s classic presentation is episodic HTN, headache, and diaphoresis; it is diagnosed with increased 24-hour urinary catecholamines, metanephrines, and/or vanillylmandelic acid followed by CT/MRI to localize the secreting neuroendocrine tumor. Treatment is surgical excision of the adrenal/extra-adrenal mass.

- **Gestational hypertension and preeclampsia:** Pregnancy-induced (after week 20 of gestation) hypertension without proteinuria is termed gestation-al hypertension; \textit{gestational hypertension} with concomitant proteinuria is termed \textit{preeclampsia}, while the addition of seizures advances the diagnosis to \textit{eclampsia}. Preeclampsia can accelerate rapidly and cause life-threatening complications for the mother and/or fetus; treatment requires parenteral therapy (intravenous magnesium sulfate for seizure prophylaxis; hydralazine and/or labetolol for HTN control) and/or emergency interventions—namely, delivery.\textsuperscript{17} Some evidence suggests that the incidence of preeclampsia can be reduced via increased intake of aspirin, ascorbate, calcium, tocopherol(s), and magnesium\textsuperscript{18}, and by pre-pregnancy treatment/cure of obesity, diabetes mellitus, and HTN. \textbf{Acute HTN of 160 mm Hg systolic or 110 mm Hg diastolic requires urgent treatment; acute-onset HTN can cause stroke at pressures generally tolerated in chronic HTN because in the latter vascular adaptations accommodate higher pressures, while in the former, the cardiovascular system has not had time to adapt, thus leaving the patient particularly vulnerable.} Acute-onset HTN from \textit{any cause} should be treated urgently when pressures approximate or exceed 160-180 mm Hg systolic or 110 mm Hg diastolic, especially \textit{but not exclusively} if accompanied by complications such as angina (test serum cardiac enzymes), shortness of breath (consider pulmonary edema and auscultate for crackles), vision changes, papilledema, headache/confusion/seizures (which suggest cerebral edema or cerebral vasospasm), proteinuria, or edema of the face, peripheral extremities, or of the general body (anasarca, check for sacral edema and weight gain).

- **Primary hyperaldosteronism** (\textit{Conn’s syndrome}): Primary hyperaldosteronism is caused by a unilateral adrenal adenoma or bilateral adrenal hyperplasia. The typical finding is HTN with hypokalemia, occasionally with slight hypernatremia, and diagnosis is by increased urine or serum aldosterone or by the more specific elevated serum aldosterone:renin ratio. Per \textit{The Merck Manual}\textsuperscript{19}, “Initial laboratory testing consists of plasma aldosterone levels and plasma renin activity (PRA). Ideally, tests are done with the patient off of drugs that affect the renin-angiotensin system (e.g., thiazide diuretics, ACE inhibitors, angiotensin antagonists, β-blockers) for 4 to 6 wk. PRA is usually measured in the morning with the patient recumbent. Patients with primary aldosteronism typically have plasma aldosterone > 15 ng/dL (> 0.42 nmol/L) and low levels of PRA, with a ratio of plasma aldosterone (in nanograms/dL) to PRA (in nanograms/mL/h) > 20.” Curative treatment is laparoscopic removal/resection of the hypersecreting adrenal tumor; for patients who are not surgical candidates, drug treatment with an aldosterone-blocking drug (i.e., spironolactone or eplerenone) is used. Pseudohyperaldosteronism can be caused by overconsumption of Glycyrrhiza glabra (licorice) because glycyrrhizin inhibits 11-beta hydroxysteroid dehydrogenase thus preventing cortisol’s inactivation to cortisone in the kidney and thereby potentiating the mineralocorticoid effect of endogenous cortisol. Another cause of pseudohyperaldosteronism is Liddle’s syndrome, a genotypic disorder causing increased sodium reabsorption, characterized by early onset (<35y) HTN with hypokalemia, low urinary sodium levels, and normal serum aldosterone levels.

- **Renal artery (renovascular) stenosis:** Classically caused by fibromuscular dysplasia in young adult women (<25y) and by atherosclerosis in older adults (>50y), renovascular stenosis is suggested by elevation of creatinine following administration of an ACEi. Diagnosis is by renal ultrasound or contrast arteriography; treatment is with stent placement, \textit{(Continued on page 185)}
Renal parenchymal disease: Renal disease can both lead to and result from HTN. Chronic HTN causes renal parenchymal damage, and parenchymal damage (whether due to HTN or another cause such as glomerulonephritis, pyelonephritis, polycystic kidneys, etc) leads to water retention and activation of the renin-angiotensin-aldosterone system, thus promoting a vicious cycle of progressive HTN and renal failure. The clinical picture commonly includes edema, elevated BUN and creatinine, anemia due to insufficient production of erythropoietin, and osteomalacia/osteodystrophy due to hyperphosphatemia, hypocalcemia, and insufficient renal formation of 1,25-dihydroxyvitamin D3. The diagnosis of renal disease is suggested by the finding of elevated BUN and creatinine on routine chemistry/metabolic panel blood tests; the diagnosis is further verified and refined by the use of CT, MRI, or US imaging, followed if necessary by renal biopsy. The Cockcroft-Gault formula has commonly been used for bedside estimation of renal function based on the patient’s age, weight, gender, and serum creatinine (sCr); the formula is provided below in two versions, one using American-favored mg/dL as the unit for sCr, and the other using the international units of micromol/L—note that the later formula employs a different constant value per gender in the numerator of the equation. The Cockcroft-Gault formula estimates creatinine clearance, which in turn is an estimate of the glomerular filtration rate (GFR), a measure of kidney function; thus creatinine clearance and GFR are somewhat interchangeable from a practical clinical perspective. Clinicians should appreciate the importance of the patient’s age in determining GFR; sCr in the upper end of the normal range may indicate renal insufficiency in a patient of advanced age.

Although the Cockcroft-Gault formula is the best known and longest used formula for the estimation of GFR, currently the best equation for more accurately estimating GFR from serum creatinine is the Modification of Diet in Renal Disease (MDRD) Study equation, which is available on-line at http://www.nkdep.nih.gov/professionals/gfr_calculators/. Finally on this topic, clinicians should be aware of measuring serum cystatin C to assess renal function. Cystatin C is a cysteine protease inhibitor produced by all nucleated cells, and its serum level is not affected by diet or muscle mass (unlike serum creatinine). The normal range for cystatin C when measured by particle-enhanced nephelometric immunoassay (PENIA) is <0.28 mg/L or <0.95 mg/L when measured by other immunologic methods. Cystatin C is a more sensitive indicator of declining renal function than is serum creatinine, and—like elevating serum creatinine or declining GFR (or elevated CRP for that matter)—cystatin C predicts risk and severity of CVD, CHF, and CKD; furthermore, cystatin C is directly involved in the pathogenesis of atherosclerosis.

Sleep apnea: Obstructive sleep apnea (OSA) is a risk factor for HTN, and treatment for OSA with continuous positive airway pressure (C-PAP) can produce modest reductions in BP that are proportionate to the severity of the HTN and compliance with treatment. Diagnosis is generally by history and physical exam confirmed with an overnight sleep study (polysomnography).

Systemic sclerosis: HTN in general and treatment-resistant HTN in particular are seen in systemic sclerosis, a disease in which cardiopulmonary disease (e.g., pulmonary hypertension, congestive heart failure) and renal compromise (e.g., acute renal crisis heralded by nephrogenic hypertension) are the most common causes of death. Abnormalities disclosed on history and physical exam may include Raynaud’s phenomenon, sclerodactyly, mask-like face, telangiectasia, and esophageal dysfunction. Laboratory findings typically include some combination of positive antinuclear antibodies (ANA), anticientromere antibodies, anti-SCL-70 antibodies, and (more rarely) anti-fibrillarin antibodies. Treatment for scleroderma and other common autoimmune disorders is reviewed in Integrative Rheumatology.

Thyroid disease, including both hyperthyroidism and hypothyroidism: Assess clinically (e.g., pulse rate, physical exam, weight loss/gain, Achilles reflex return speed, body temperature), and with laboratory testing: serum TSH, free T4, free T3 and/or total T3; strongly consider testing reverse T3 when assessing for functional hypothyroidism. Some integrative

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clinicians—including the current author—hold that the ratio of total T3 to reverse T3 should be >10:1.22

- **Tobacco use:** Tobacco smoke constituents cause arterioconstriction which promotes HTN. Constituents and free radicals in tobacco smoke are more pathogenic than nicotine, while the latter in isolation indeed causes adverse cardiovascular effects.

- **Upper cervical spine dysfunction/subluxation:** A remarkable clinical trial published in Journal of Human Hypertension in 2007 by Bakris et al23 showed that correction of upper cervical spine subluxation/dysfunction by chiropractic spinal manipulation causes “marked and sustained reductions in BP [blood pressure] similar to the use of two-drug combination therapy.”

- **Vitamin D deficiency:** Vitamin D deficiency is common in the general population—often up to 90-100% of subjects in large population-based studies—and causes intracellular hypercalcinosis24 via elevated PTH levels and contributes to chronic HTN25 via endothelial dysfunction, systemic inflammation, insulin resistance, and activation of the reninangiotensin-aldosterone system.26 Correction of vitamin D deficiency can cause a reduction in elevated blood pressure comparable to that which can be achieved by single-drug oral antihypertensive medication27 while also providing numerous collateral benefits (including reductions in depression, pain, and risks for autoimmune and malignant diseases) at lower cost and greater safety than can be achieved with pharmaceutical drugs.28,29

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