DRUG-INDUCED HYPERTENSION

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CASE PRESENTATION

- J K female patient 30 ys old married housewife has 3 offsprings, ch. heavy smoker.
- She took oral contraceptive pills 9 ms ago.
- She has no other medical problems.
- She came to internal medicine outpatient clinic C/O of frontal headache, dizziness, & fatigue.
- FH of HTN of her mother & grand sister, her father died from cerebral stroke (HAGE).
- On examination she is overweight, BMI 28.
- BP 180/100mgHg.
- No other important clinical manifestations.

Differential Diagnosis of Hypertension

Common:

- Essential HTN.
- False ↑ as inadequate BP cuff size.
- White coat HTN.

Most consider:

- Renal HTN
- Renovascular HTN
- Conn's syndrome
- Phaeochromocytoma
- Coarctation of the aorta

Other Causes:

- Cushing's syndrome
- Acromegaly
- Polycystic ovarian syndrome
- Drug induced HTN.

INVESTIGATION

- CBC
- FBG
- S.NA, S.K
- Lipid profile.
- S.UA
- BL. urea, s. creatinin
- ALT, AST, S. albumin
- Urinalysis
- ECG, ECHO, chest X-ray
- Abdomino-pelvic U/S & Doppler exam.
- ALL are normal.

What is Drug-Induced Hypertension?

- The human heart is responsible for pumping fresh, oxygen-rich blood to various organs of body through a system of arteries. BP refers to the pressure with which blood flows through these vessels.
- Hypertension ➔When this pressure exceeds the normal upper limit of flow pressure.
- There are two components of blood pressure:
  - Diastolic b p: pressure with which blood flows in the arteries, when heart is relaxed.
  - Systolic blood pressure: The pressure flow, when heart pumped blood into arteries
  - Normal: Systolic BP less than 120; diastolic BP less than 80mmHg
  - Prehypertension: Systolic BP between 120-139; diastolic BP between 80-89 mmHg.

Secondary hypertension

- High BP caused by a medical condition. HTN ➔ in individuals ≤ 65 ys, a secondary cause should be ruled out
- Drug-Induced Hypertension is a type of 2ry HTN caused by a variety of therapeutic agents; either transient or persistent
- Usually, it is of a transient nature, a careful evaluation of the individual's drug regimen may identify offending drug.
- Common signs and symptoms: headache, light-headedness, nausea, vomiting, muscle tremors, and excessive sweating.
- Complications of HTN may develop over a long time,➔ an in-adequate blood flow to various body organs.
- Stoppage of the responsible drug ➔ control symptoms.
- The prognosis is very good, with appropriate management.

Who gets Drug-Induced Hypertension?

- It affect any individual taking medications that can cause HTN.
- ♂ >♀
- Worldwide; all racial and ethnic groups can be affected.

What are the Risk Factors for Drug-Induced Hypertension?

- More common in individuals with impaired NA excretion because of kidney dysfunction.
- Drugs: corticosteroids, oral contraceptive pills, cyclosporine, NSAIDs and antidepressants, are known to ↑the BP.
- The deleterious effect of therapeutic agents is more in patients with preexisting HTN, kidney failure, elderly adults.
- Rebound hypertension occurs when drugs that lower one's BP are discontinued or stopped.
- Absence a risk factor does not mean that an individual will not get the condition.

Causes of Drug-Induced Hypertension

- DIH ➔ due to an intrinsic pressor effect of the drug (chemical nature), /an interference with the CV control system by causing the CVS to ↑ BP.
- Some drugs ➔ cause NA retention by the kidneys, or extracellular volume expansion (eg. contraceptives pills).
- The hypertensive effect of NSAIDs is dose dependent ➔ inhibition of COX-2 in the kidneys, which ↓ NA excretion and↑ intravascular volume.
- HTN, a common adverse effect of EPO ttt in CKD patients by ↑↑ Hb concentrations
- Cyclosporine ➔ release of vasoconstrictors.

The Signs and Symptoms of DIH

- DIH manifested when BP is very high, due to ↓ in the blood supply to important organs.

- Extremely high values of BP (systolic > 220 mm Hg and diastolic > 120 mm Hg)➔ any of the following conditions:

- **Hypertensive urgency:** very high BP, without any organ damage.
- **Hypertensive emergency**: very high BP with evidence of organ damage.

Signs and Symptoms

- Headache: due to a ↓ supply of nutrients, bleeding in the brain.
- Nausea and vomiting
- Anxiety
- Excessive sweating
- Muscle tremors
- Altered mental status
- Light-headedness, which may progress to black-outs
- Changes in visual acuity, causing vision defects
- Chest pain ➔↓ blood supply to the heart decreases,
- Urinary symptoms ➔ damage to kidney vessels,➔hematuria
- Palpitations

How is D I H Diagnosed?

- A diagnosis➔ patients take drugs known to cause HTN, presence of certain signs and symptoms.
- Once an elevated reading of BP is obtained, repeated at minimum of 3 times ➔classify hypertension.

- Other tests ➔ eliminate other probable causes of HTN:
  - Blood tests ➔ s. NA, K.
  - Urinary tests to detect any kidney disorders.
  - Blood sugar levels.
  - ECHO ➔ any abnormality in the structure of heart
  - Ultrasound of the kidneys ➔ any abnormal bl. flow, structure of the kidneys.
  - Comprehensive eye exam.
  - Brain CT (in case of hypertensive emergencies)
  - ECG ➔ effects of high BP on the heart.

Possible Complications of D I H

- Effects on the heart:
  - With long-standing HTN ➔ left ventricular hypertrophy ➔ ↑load on heart
  - Heart attack or even heart failure
- Effects on the eye:
  - Untreated high BP ➔ a sequence of changes in the eye ➔ damage of the retina.
  - This may eventually end-up as blindness,(irreversible).
- Effects on the brain:
  - BP ➔ cerebral hemorrhage.
  - A stroke ➔ permanent neurological defects.
- ↑ BP and smoking ➔ increased risk of developing vascular aneurysm (weakening of the vessel wall).
- The blood vessels may rupture and cause uncontrolled bleeding.

How is DI H Treated?

- The physician may adjust the ttt of current drug causing high BP. If required,➔ stopped.
- Lifestyle modifications:
- Weight loss: It is the most important factor in the management.
- Smoking cessation
- Reduced alcohol intake
- Regularly exercising and consuming a low-fat, low-salt diet
- Medications used to lower blood pressure may include:
  - Alpha blockers, Beta blockers
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Angiotensin receptor blockers (ARBs)
  - Calcium channel blockers
  - Central alpha agonists
  - Diuretics

How can D I H be Prevented?

Various ways to avoid developing HTN include:

- ✓Maintaining a healthy weight
- ✓Eating a diet low in salt, sugar, and fat
- ✓Exercising regularly
- ✓Smoking cessation
- ✓Limiting the intake of alcohol
- ✓Taking the prescribed medications regularly
- ✓Managing stress using relaxation techniques
- ✓Closely monitoring individuals treated with medications that may ↑ BP.
- ✓Generally, the BP will return to normal levels after discontinuation of the medication.

What is the Prognosis of D I H?

- D I H is reversible, a good prognosis if identified early.
- Early diagnosis and management of HTN prevent grave complication.
- Once complications develop, ?? irreversible; prognosis is dependent upon the extent of organs damage.
- The greater the duration of ↑ BP, greater the level of HTN, ➔poorer prognosis;(if not treated well).

Medication that may increase the blood pressure:

- Amphetamines, cocaine
- Corticosteroids
- Cyclosporine
- Erythropoietin
- Oral contraceptive pills
- Antidepressants such as MAO inhibitors
- Migraine medications

Sympathomimetic Agents

- IT is established sympathomimetic amines cause dose-related ↑BP.
- This is insignificant in healthy patients but hazardous in others.[1-4]
- Include; amphetamines and similar compounds, ephedrine, pseudoephedrine, phenylpropanolamine.
- These are contained in some OTC cough and cold preparations.
- Phenylpropanolamine, FDA banned it from the market.[3,4] Because of correlation with HTN & stroke.
- Pseudoephedrine, a bronchodilator and nasal vasoconstrictor, is safe in recommended doses. for its potential misuse, it was restricted to behind counter ➔ should be avoided in HTN patients.

- Twenty-four clinical trials included 1,285 patients ➔ pseudoephedrine causes a small mean↑in systolic BP (1 mmHg), with no significant effect on diastolic BP, a slight ↑ in HR(3 beats /minute), a dose-related
- Immediate-release formulations had a greater effect than sustained-release formulations.
- ♀ are slightly less susceptible to the CV effects.
- Controlled HTN, it increases systolic BP only, no effect on HR in as many patients took beta-blockers.
- No significant AEs, such as hypertensive emergencies, stroke, or arrhythmia .[6].

- CNS stimulants; dextroamphetamine, methamphetamine, and methylphenidate (related to amphetamine) used for narcolepsy and attention-deficit/hyperactivity disorder
- The FDA ➔ using CNS-stimulant (dextroamphetamine) at usual doses in children, adolescents, adults with serious heart problems / structural cardiac abnormalities ➔associated with sudden death.[8]
- Generally, amphetamine-related compounds ➔ avoided in patients with structural cardiac abnormalities; cardiomyopathy, serious heart rhythm [9] ,
- Potential CV risk (↑ HR,BP) should be balanced against the beneficial behavioral effects of these medications.

NSAIDs and COX-2 Inhibitors

- NSAIDs have potentially AEs on kidney in 1-5% of its users.[13]
- NSAIDs block both COX-1, COX-2 enzymes ➔ ↓prostaglandin (PGs) formation.[10,11]
- Dose-related ↑ in NA and H2O retention.
- Normal kidney, COX-1 in the glomerulus and afferent arteriole and COX-2 in the afferent arteriole, the podocytes, and macula densa.[12] .
- PGs produced by COX-1 affect renal homeostasis by vasodilation ➔ ↓ renal vascular resistance, ↑ renal perfusion.
- PGs produced by the COX- 2 have diuretic and natriuretic effects.[12,13]
- In hemodynamically compromised patients, both isoenzymes are essential for maintenance of renal perfusion.

- Additionally, production of vasoconstricting factors, endothelin-1➔ ↑ BP in a normotensive or controlled HTN patient.[14]
- Both selective, non selective NSAIDs ➔ CV and renal side effects in 27.8%, with HTN 16.6%.[14]
- There was no statistical difference in the incidence of HTN between the traditional NSAIDs and COX-2 groups, that may?? greater HTN.
- Rofecoxib was voluntarily pulled from the market in 2004 due to↑ risk of heart attack and stroke.[17]
- Patients with HTN should closely monitored on using NSAIDs.
- This AE should be considered in the elderly; high prevalence of arthritis, HTN and NSAIDs use.[18]

Corticosteroids

- All corticosteroid drugs, including prednisone, result in dose-related NA & H2O retention.[19] ➔overstimulation of the mineralocorticoid receptors in kidney.
- CS with strong mineralocorticoid effects, fludrocortisone and hydrocortisone, ➔ the greatest amount of fluid retention.
- CS lack significant mineralocorticoid activity, dexamethasone, triamcinolone, betamethasone ➔ minor fluid retention.[20]
- ↑NA & H2O may cause HTN / worsening BP control.
- CS-IH respond to diuretic therapy.[21]
- The smallest effective dose and shortest duration of steroid therapy should be used to ↓ this adverse effect.
- Fludrocortisone is useful in treating patients with postural HTN but was poorly tolerated in elderly patients.

Caffeine

- The effects of caffeine on BP control are not well defined.
- A meta-analysis of RC trials analyzing the effect of either coffee or caffeine alone on BP levels[23]
- An increase of 2.04 mmHg in systolic BP and of 0.73 mmHg in diastolic BP.
- BP elevations induced with caffeine (410 mg/day) more than with coffee (725 mL/day).
- The effects of coffee and caffeine on HR were not significant.

Estrogens and Progestins

- Chronic use of oral contraceptives may slightly ↑ BP and other CV effects in certain women .
- Using high-dose estrogen((≥50 mcg), & progestin dose (1 -- 4 mg).[➔ ↑ of 3 - 6 mmHg systolic and 2 -- 5 mmHg diastolic, 5% of women developing new HTN (a dose-dependent fashion) .[24]
- Occur more in patients with previous gestational HTN, smokers, with FH of HTN.
- Usually, the rise in BP is mild, malignant HTN can occur.[25]
- Cessation of therapy ➔ a return to baseline BP within 2-- 12 Ms, but proteinuria may persist.[25,26]
- Mechanisms are poorly understood. ?? renin-angiotensin system as it ↑ the hepatic production of the renin substrate.[27]
- Current preparations contain as little as 20% of the amount of estrogen and progestin than previous ones.
- Postmenopausal ERT, or HRT have a neutral effect on BP.[30] .
- HRT may➔ slow ↑ in systolic pressure over a longer period], significant ↑ in CVD, venous thromboembolic ➔ no longer recommended for CV protection.[35]

Dietary Supplements

- Ginseng is generally safe supplement and associated with few serious AEs.
- It have a mild CNS stimulant effect, should be cautioned if used with other stimulants in patients with CV disease.
- A ginseng abuse syndrome; diarrhea, HTN, nervousness, dermatologic eruptions, and insomnia, has been described.[36]
- This syndrome may be exhibited after single high doses or prolonged periods of use.
- Other supplements that may increase BP include natural licorice and yohimbine.[37]
- All patients with HTN should discuss use of dietary supplements with physician.

Serotonin-norepinephrine Reuptake Inhibitors

- Venlafaxine, a SNRI used in ttt of depression and anxiety disorders.
- Mechanism of HTN ➔ ↑ levels of norepinephrine ➔ potentiation of noradrenergic neurotransmission.[38]
- The extended-release formulation with normal doses (75-150mg) ↑ BP mildly in 3% of patients).[38].
- Doses(≥300 mg) of extended-release ➔ significant ↑ BP (10 and 15 mmHg) in 13% of patients,.[39] However, usually not warrant discontinuation of drug.[40

- Sibutramine is an SNRI, chemically similar to amphetamine, ➔ ↑ BP in both normotensive and hypertensive patients due to ↑ amount of norepinephrine.[41
- Sibutramine (10 --15 mg) ➔ a mean ↑ of systolic and diastolic BP of 2 mmHg in normotensive patients.[43,44]
- Patients with HTN ➔ sign. higher elevations in BP.
- Not used in patients have CV disease; HTN, functional abnormalities, and CVD.

Immunosuppressants

- The adverse effect of cyclosporine on BP is well known.[45]
- Several hypotheses have been proposed, including increased PG synthesis and ↓H2O,NA,K excretion.[46,47]
- Up to 50% of renal transplant patients receiving cyclosporine ➔ ↑ BP.[48].
- CIC is not discontinued for HTN in transplant patients & autoimmune disease.
- CIC I-HTN ttt; pharmacologic, Ca channel blockers, diuretics, beta-blockers, or ACE inhibitors, or non pharmacologic, ↓ NA intake.[45]
- CIC dose should be ↓ 25%.[48] BP should be monitored every two weeks for the first three months of ttt.
- In patients with severe, refractory HTN,? switching to tacrolimus.
- Tacrolimus ↑ BP in 35% of patients > that of cyclosporine (50%).[49]
- The mechanism& managment of tac-induced HTN is postulated to be similar to cyclosporine's.[50].
- Careful BP monitoring is needed during therapy.

HOME MESSAGE

- Physicions should maintain an awareness of the major drug classes that may ↑ BP /or interfere with its effective control.
- D I H include sympathomimetics, NSAIDs, estrogens, corticosteroids, cyclosporine, and some natural products (e.g., ginseng).
- Physicion should screen for medications that↑ BP and provide feedback to patients to ↓ this cause of 2ry HTN.
- All patients with HTN should be monitored more closely when new medications are added, especially drugs known to↑ BP.

References and Information Sources

http://www.nlm.nih.gov/medlineplus/ency/article/000155.htm (accessed on 8/16/2015)
http://www.ncbi.nlm.nih.gov/pubmed/22195528 (accessed on 8/16/2015)
http://www.neurology.org/content/56/9/1210 (accessed on 8/16/2015)
http://www.mayoclinic.org/diseases-conditions/secondary-hypertension/basics/causes/con-20033994 (accessed on 8/16/2015)

Helpful Peer-Reviewed Medical Articles:

Grossman, E., & Messerli, F. H. (2012). Drug-induced hypertension: an unappreciated cause of secondary hypertension. Am J Med, 125(1), 14-22. doi: 10.1016/j.amjmed.2011.05.024

Tiurenkov, I. N. (2002). [Drug-induced hypertension and hypertensive crisis]. Klin Med (Mosk), 80(9), 18-21.

Tokudome, G., Sugano, N., & Hara, Y. (2004). [Drug-induced hypertension]. Nihon Rinsho, 62 Suppl 3, 544-549.


Thank you