SEMINAR ON PERIOPERATIVE ENDOCRINE MANAGEMENT OF PITUITARY ADENOMAS

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HORMONES SECRETED BY THE PITUITARY

- PROLACTIN
  GROWTH HORMONE
  ANT. PITUITARY
ADRENOCORTICOTROPIC
  HORMONE
  THYROID STIMULATING
  HORMONE
  GONADOTROPHIC HORMONES
  LH
  FSH
- POST. PITUITARY
  ANTI DIURETIC HORMONE
  OXYTOCIN

Ant. Pituitary hormones are under the trophic influence from hypothalamus through

corticotropin releasing hormone (CRH)

thyrotropin releasing hormone (TRH)

dopamine – inhibitory to prolactin

somatotropin releasing hormone

gonadotropin releasing hormone

CLASSIFICATION OF PITUITARY ADENOMAS ACCORDING TO ENDOCRINE FUNCTION

ADENOMAS WITH GH excess

PRL excess

ACTH excess

TSH excess

FSH / LH excess

PLEURI hormonal adenomas

ADENOMAS WITH NO APPARENT HORMONAL FUNCTION

ASSESSMENT OF PITUITARY FUNCTION

- BASAL TESTING : serum levels of
  - prolactin
  - ACTH
  - cortisol
  - GH
  - FSH/LH
- DYNAMIC TESTING – to test for impaired reserve capacity

TESTS FOR SOMATOTROPIC FUNCTION

- Growth hormone levels in the fasting state and after administration of stimulatory or inhibitory agents
- Stimulatory tests :

  Insulin induced hypoglycemia- after IV administration of 0.1-0.15IU/Kg of plain insulin GH level >5ng / ml indicates normal function

  it is avoided in elderly, those with cerebro vascular disorders or convulsive disorder

  other agents like – Arginine, clonidine, propranolol, L-dopa

TESTS FOR SOMATOTROPIC FUNCTION

- Elevated levels of Somatomedin-C (Insulin Like Growth factor – IGF-1) : always elevated in acromegaly
- Failure of suppression of elevated levels of GH to < 2ng / ml after glucose loading

TESTS FOR THYROTROPIC FUNCTION

- T3 , T4 , TSH levels
- If TSH levels are normal in the presence of low T3 / T4 levels then TRH reserve is tested
- 200 micro grams of TRH is given IV – if TSH is elevated to > 6-20 micro units / ml –normal

  absence of response – total hypophysectomy
- Decreased response occurs in thyroid hormone therapy, glucocorticoid therapy, hyperthyroidism, renal failure, depression

PROLACTIN FUNCTION

- Serum prolactin levels (normal 5-20ng / ml)
- Stimulation tests – TRH, chlorpromazine, metoclopramide
- Suppression tests – L-dopa, nomifensine
- Dynamic tests are not used if prolactin levels > 150ng / ml or tumor is found on MRI / CT
- Used if prolactin levels are mildly elevated and MRI findings are equivocal

PROLACTIN FUNCTION

ELEVATED PROLACTIN LEVELS

- Physiological – pregnancy, lactation
- Pharmacological – psychotropic drugs,
  antihypertensives
  high dose estrogens
- Pathological – hypothyroidism
  chronic renal failure
  hepatic diseases
  cushings disease`

EVALUATION OF HPA AXIS

- CUSHING`S disease – hyper secretion of cortisol caused by abnormality of pituitary gland
- CUSHING`S syndrome – general syndrome caused by excess cortisol levels

EVALUATION OF HPA AXIS

- Serum cortisol level
- 24 hr urine collection for free cortisol (>100micrograms / 24 hrs)

  17 hydroxy corticosteroids

  (>12mg /24 hrs)
- Suppression of cortisolemia

  rationale

  1mg overnight dexamethasone test

  low dose oral dexamethasone test (0.5mg qid)

  high dose oral dexamethasone test (2mg qid)

EVALUATION OF HPA AXIS

- CORTISOL DYNAMICS – DIURNAL RHYTHM - highest at 8 a.m.

  lowest at 6 p.m
- Plasma ACTH levels
- CRH test (to differentiate pseudo / cyclical cushings)

EVALUATION OF HPA AXIS

- Non stimulated serum cortisol level at

  8 a. m.

  if > 18 micrograms / dl (normal function)

  if < 3 micrograms / dl (adrenal insufficiency)
- If levels are low then ACTH test is necessary
- If levels 3.1 – 17.9 micrograms / dl then dynamic testing is necessary

EVALUATION OF HPA AXIS

	ITT	METYRAPONE	CRH	Conventional Dose ACTH	Low Dose ACTH
Stimulus	Insulin 0.1-0.5 iu/kg IV	Metyrapone 30mg/kg by mouth at midnight	Ovine CRH 1 micro gm/kg IV	1-24ACTH 250 micro gm IV/IM	1-24 ACTH 1 micro gm IV
Blood drawing time	30,45,60 and 90 min	8 am s.cortisol next day	15,30,60 min	30,60 min	30 min
measurements	s.cortisol,bld glucose	s.cortisol,11deoxy cortisol	s.cortisol	s.cortisol	s.cortisol
Cut off	s.cortisol >18microgm/dl, if glucose <40mg/dl	s.cortisol <5microgm/dl, 11deoxycortisol >7microgm/dl	>18.5microgm/dl	>18microgm/dl	>18microgm/dl

GONDOTROPH FUNCTION

CRITERIA :

- Absence of other hormonal abnormality
- Elevated basal and stimulated response of gonadotropins

GONADOTROPH FUNCTION

	men	WOMEN
Increased Basal Conc. of	FSH Alfa ,LH-beta,FSH-beta LH+testosterone	FSH but not LH FSH and estradiol Any subunit relative to intact FSH AND LH
Increased response to TRH	FSH LH LH-beta	FSH LH LH-beta

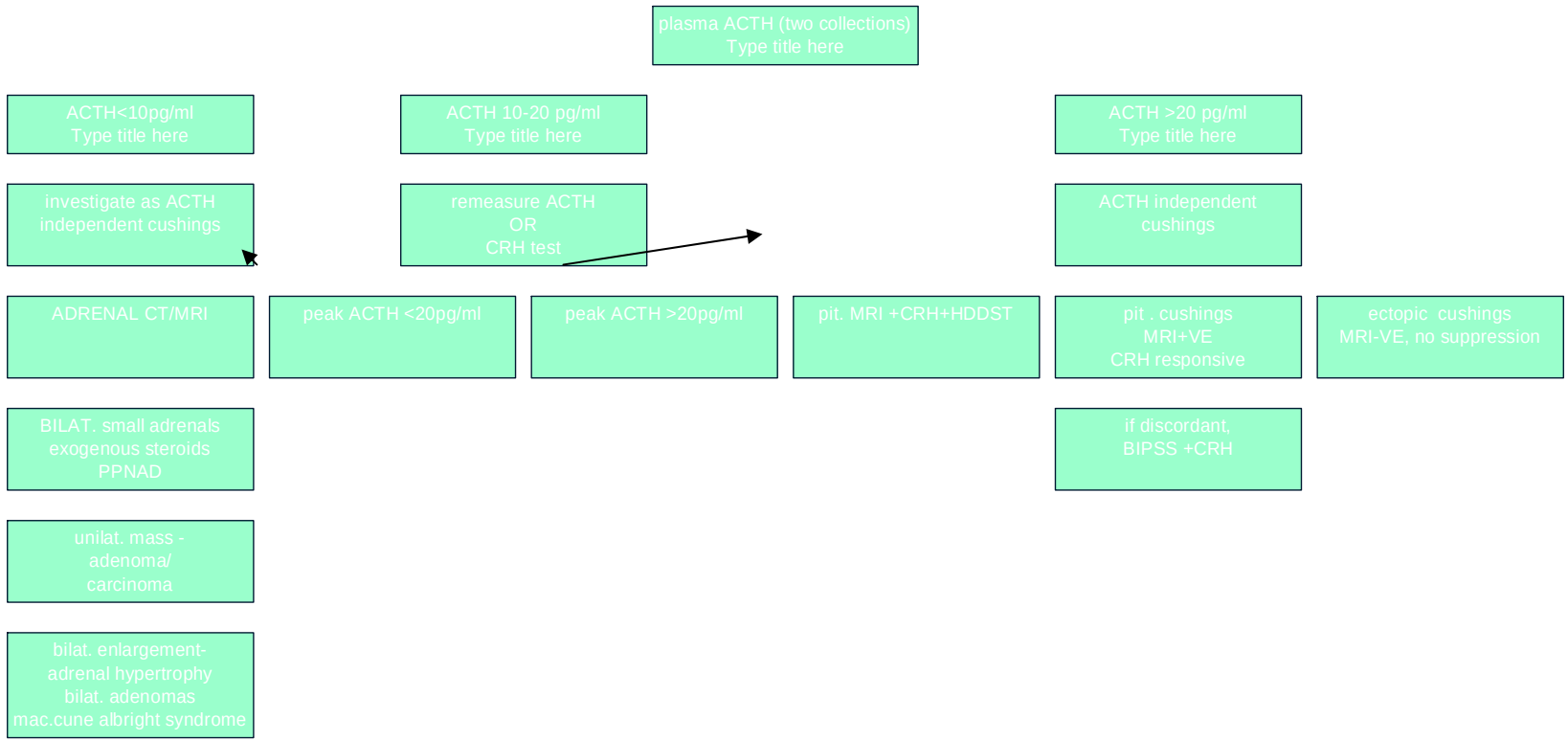
EVALUATION OF SUSPECTED CUSHING`S SYNDROME

- HISTORY- increased weight, growth retardation in children , weakness, easy bruising, stretch marks, poor wound healing, fractures, change in libido, impotence, irregular menses, mood changes
- EXAM – fat distribution, hypertension, proximal muscle weakness, thin skin and ecchymosis, purple striae, hirsutism, acne, facial plethora, edema

EVALUATION OF SUSPETED CUSHING`S SYNDROME

- LAB findings – abnormal glucose tolerance, frank DM , hypokalemia
- 1st line screening tests – elevated 24hr
  urinary free cortisol (3
  collections)
  lack of suppression to LDD
  increased late night salivary cortisol
- Additional screening tests –
  cortisol circadian rhythm
  insulin tolerance test
  combined LDDST + CRH test

D /D OF CUSHNG`S SYNDROME



MEDICAL TREATMENT OF CUSHINGS

Preoperatively –

- Agents that modulate adrenocorticotropin release – restricted to treatment of ACTH dependent cushings

  - serotonin antagonists : cyproheptadine, ritanserine - rarely used

  - dopamine agonists - bromocriptine,
    cabergoline

  -sodium valproate

  - somatostatin analogues – octreotide, lanreotide

- Agents decreasing adrenal steroidogenesis

  mitotatane, metyrapone, ketoconazole, aminoglutethemide, trilostane, etomidate

- Glucocorticoid receptor antagonists – mifepristone

Used to achieve eucortisolemia for 4-6 wks before surgery

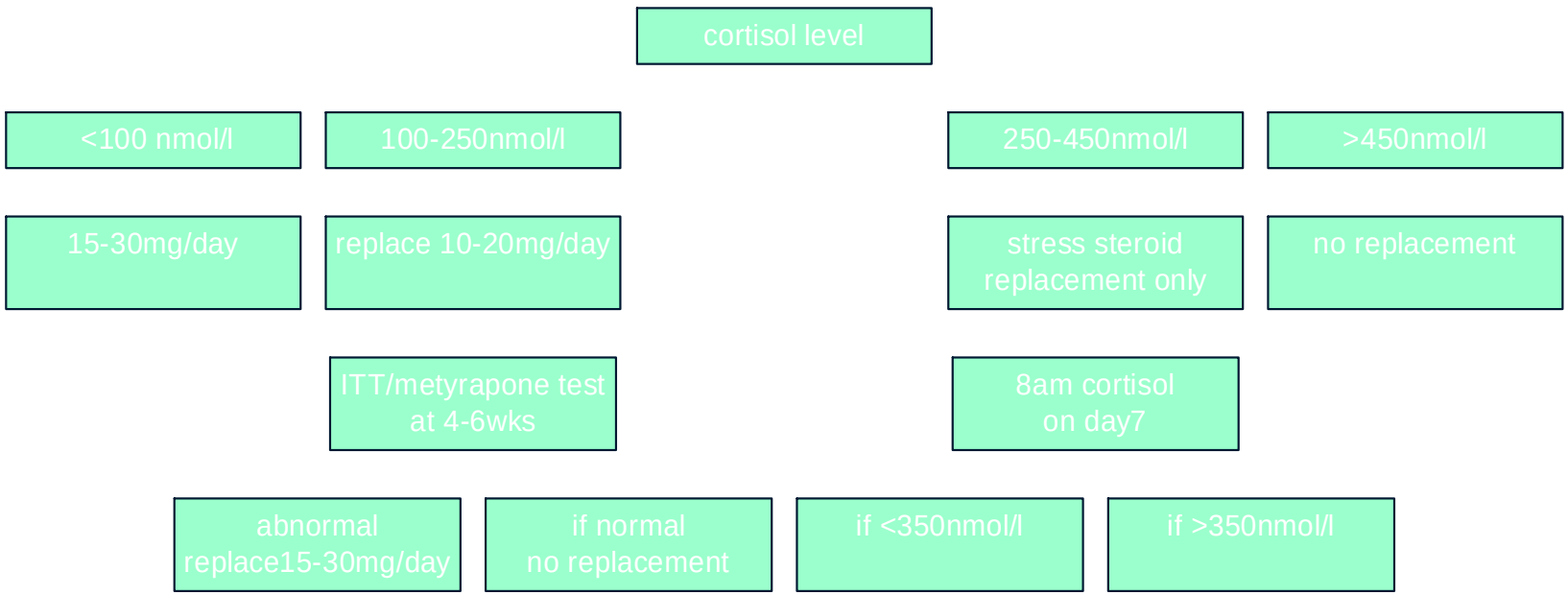
Postoperative steroid replacement

Pit adenoma for surgery is tested for

8 am cortisol levels and ACTH 1-24 test

- If normal no peri operative steroids are given and serial 8 am serum cortisol levels are checked on pod 1-3
- If abnormal, patients are given 48 hrs post operatively with supra physiological doses of hydrocortisone / dexamethasone and 8am s.cortisol levels are checked on day 3-5

Post operative steroid replacement



ACROMEGALY

- Pre op medical treatment with somatostatin analogue octreotide and dopamine agonist bromocriptine is not used commonly as dose requirements are higher, increased incidence of side effects
- They are used in case of persistence of active acromegaly inspite of surgery or radiotherapy
- Indications of recurrence after surgery are rise in IGF 1 level or return of paradoxical response of GH to glucose loading

- prolactinomas

  Indications for bromocriptine therapy

  – Pt with a non invasive prolactinoma and a serum prolactin level between 150-500ng/ml
  – Pt with serum prolactin level >1000ng/ml
  – Woman with microprolactinoma and a modestly elevated prolactin level (<150ng/ml)who desires pregnancy
  – Residual / recurrent prolactinoma following surgery

prolactinomas

Criteria for cure

- Normal prolactin level
- Asymptomatic
- Negative MRI study for 5 years
- If prolactin level is <100ng/ml and shows no tendency to rise is indicative of stalk damage

Pre operative hormone therapy

Specifically in cases of

- Hypothyroidism
- Adrenal insufficiency
- Rarely hyperthyroidism
- Diabetes mellitus
- Diabetes insipidus

most important tests are

- ACTH reserve
- Thyroid function
- Electrolyte balance

Pre operative hormone therapy

Pre op replacement

- Partial or complete ACTH deficiency requires replacement with hydro cortisone /

  dexamethasone 10mg on pre op day and 10mg at the time of induction

All patients undergoing surgery for micro adenoma are given hydrocort 100mg the night before surgery and along with pre medication

Pre operative hormone therapy

- Hypothyroid patient :

  assess adrenal reserve

  correct adrenal insufficiency

  thyroid hormone replacement with

  sodium-l-thyroxine 0.75-0.2mg/day

  for 4-6 weeks till euthyroidism is

  achieved
- DM – appropriate insulin therapy
- DI – vasopressin / DDAVP therapy

Intra operative hormone therapy

- IV dexamethasone 10mg in early stages of surgery repeated after 4 hours
- Correction of fluid deficits

Immediate post op replacement

Pituitary adrenal dysfunction

- All patients are given post op steroids
- Dosage rapidly tapered and stopped after 48-72hrs in case of micro adenoma. Repeat hormone assay is done after 4-6 wks and replacement is given if necessary
- In case of macro adenoma maintenance dose of 7.5 mg of prednisolone or 0.75mg of dexamethasone is given for 4-6wks. Cortisol assay is done after stopping steroids for 2 days and further decision regarding continuing steroids taken
- In cushing`s disease – as discussed earlier

Immediate post op replacement

Pituitary thyroid dysfunction

- If euthyroid preop , no replacement is required
- If hypothyroid pre op , thyroxine replacement is continued post op. adrenal reserve function is tested and steroid replacement is given as necessary

Chronic pituitary hormone therapy

pituitary adrenal dysfunction

- HPA function is tested 4-6 wks after surgery
- Steroids are discontinued for 48 hrs prior to testing
- ACTH 1-24 testing in case of adrenal gland unresponsiveness
- if poor response then further HPA axis testing is deferred and patient maintained on replacement steroids
- If severely deficient pre op/ in case of total hypophysectomy life long replacement is given.
- Post RT maintanance dose is doubled and HPA axis testing is delayed for 6 months

Chronic pituitary hormone therapy

- Pituitary thyroid dysfunction :

  thyroxine replacement at the dose of 0.1-0.2mg/day

Chronic pituitary hormone therapy

HYPO GONADISM

- Gonadotropin assay, prolactin level and testosterone levels are assessed
- Sperm count in c/o males and menstruation with e/o ovulation in female is evidence of fertility
- For decreased libido

estrogen+1/4th dose of testosterone for females

testosterone and dopamine agonist for males

Hypo gonadism

- Chronic replacement therapy

200-300 mg testosterone proprionate IM every 2-4 wks in men

Ethinyl estradiol and medroxy progesterone acetate combination in women

For infertility, sequential combination of human menopausal gonadotroin and human chorionic gonadotropin in patients who have undergone total hypophysectomy

DIABETES INSIPIDUS

- Polyuria secondary to water diuresis and poly dipsia
- Due to low levels of ADH
- High output of dilute urine
- Craving for water, especially ice cold water
- Incidence 9.2% in micro adenoma surgery

  37% in c/o total hypophysectomy
- Mostly due to extreme sensitivity of hypothalamic neurohypophyseal unit to local alterations in blood flow, edema and traction on pituitary stalk and is transient
- Permanent disturbance of ADH secretion – direct damage to neuro hypophyseal unit

Diabetes insipidus

Types of presentation

- Transient polyuria starting 1-3 days after surgery and lasting for 1-7 days ; local edema and traction on pituitary stalk
- Triphasic response

  - polyuria beginning 1-2 days after surgery lasting for 4-5 days
  - normalization of urine output / SIADH like water retention 4-5 days
  - return of poly uria
- Transient polyuria begining immediate post op
- Permanent polyuria beginning immediate post op and continuing without any interphase

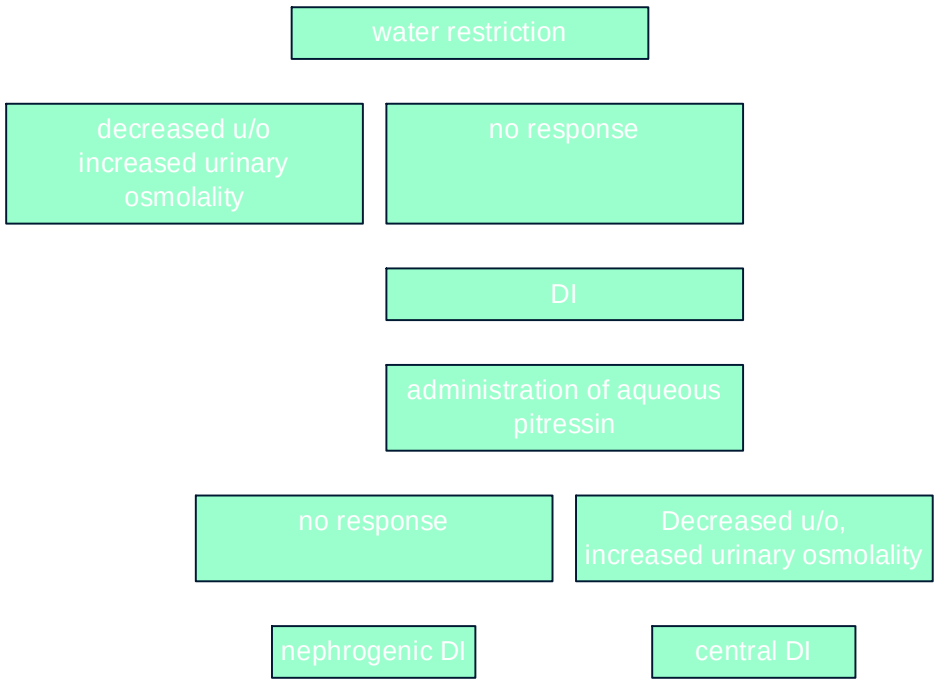
Diabetes insipidus

DIAGNOSIS

- Urine output >250ml/hr (>3ml/kg/hr in pediatric patients)
- Urinary s.g. <1004
- Urinary osmolality <200mosm/kg
- Normal or above normal serum sodium level
- Normal adrenal function

Diabetes insipidus

Diagnosis : water deprivation test(if urinary osmolality is <250mosm/kg



Diabetes insipidus-treatment

- Depends on : pts clinical status
  urine volume
  concentration of serum electrolytes
  creatinine
- If alert, with intact thirst, mild DI,
  pt can self regulate water intake
  DDAVP – nasal spray 2.5micro gm BD
- If thirst mechanism is impaired
  -meticulous I/o records
  - daily wt measurement
  - frequent electrolytes , urea , hematocrit
  - supplementation of free water
  - vasopressin analogues

Diabetes insipidus-treatment

- If consciousness is impaired
  - hrly I/o, urinary sg
  - 4 hrly electrolytes
  - parenteral fluids
  - titrated dosages of desmopressin-2-4microgm IV/SC in 2 divided doses

Chronic DI

- Rare in c/o trans sphenoidal surgery
- Treatment of choice is DDAVP
- Other drugs -clofibrate 500mg 2-4 times/d
  - chlorpropamide – 50-500 mg/day
  - carbamazepine 400-600mg/day

SIADH

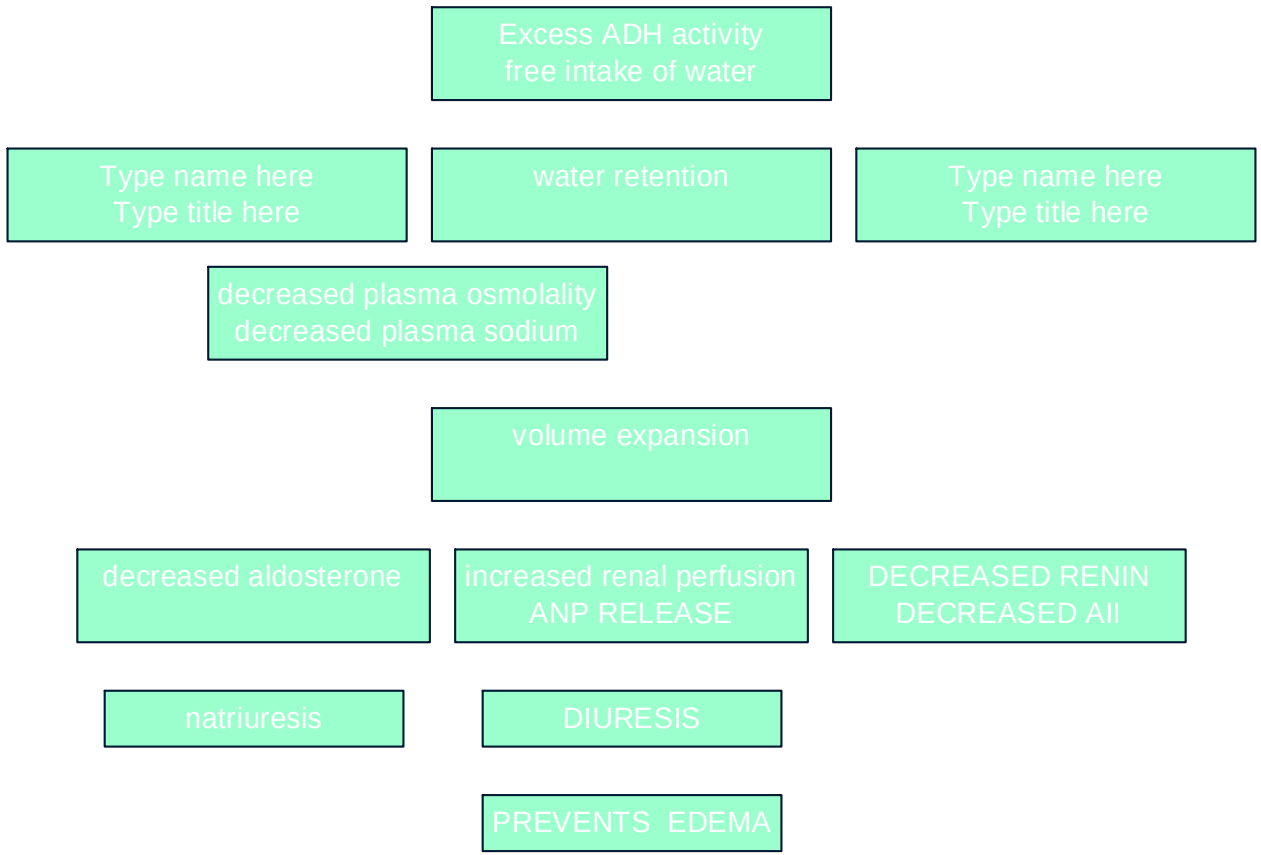
- Less common
- Causes - preop medications

  -anaesthetic agents

  -surgical stress

  - surgical irritation of neurohypophyseal unit

SIADH


Excess ADH activity
free intake of water
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water retention
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decreased plasma osmolality
decreased plasma sodium
volume expansion
decreased aldosterone
increased renal perfusion
ANP RELEASE
DECREASED RENIN
DECREASED AII
natriuresis
DIURESIS
PREVENTS EDEMA

SIADH

DIAGNOSTIC CRITERIA

- Hyponatremia
- Inappropriately concentrated urine
- No e/o renal /adrenal dysfunction
- Low serum osmolality
- No hypothyroidism
- No e/ dehydration/overhydration
- Water load test
- Symptoms – of hypo natremia

SIADH

TREATMENT

- ACUTE SIADH : fluid restriction 0.5-1.5 litres/day
- If sodium levels<120meq/l –hypertonic saline+furosemide diuresis
- Correction rate of 0.5meq/hr
- CHRONIC SIADH :

  -long term fluid restriction

  demeclocycline-150-300mg q 6hrs

  furosemide 40 mg OD

  lithium

  phenytoin