DIABETES INSIPIDUS

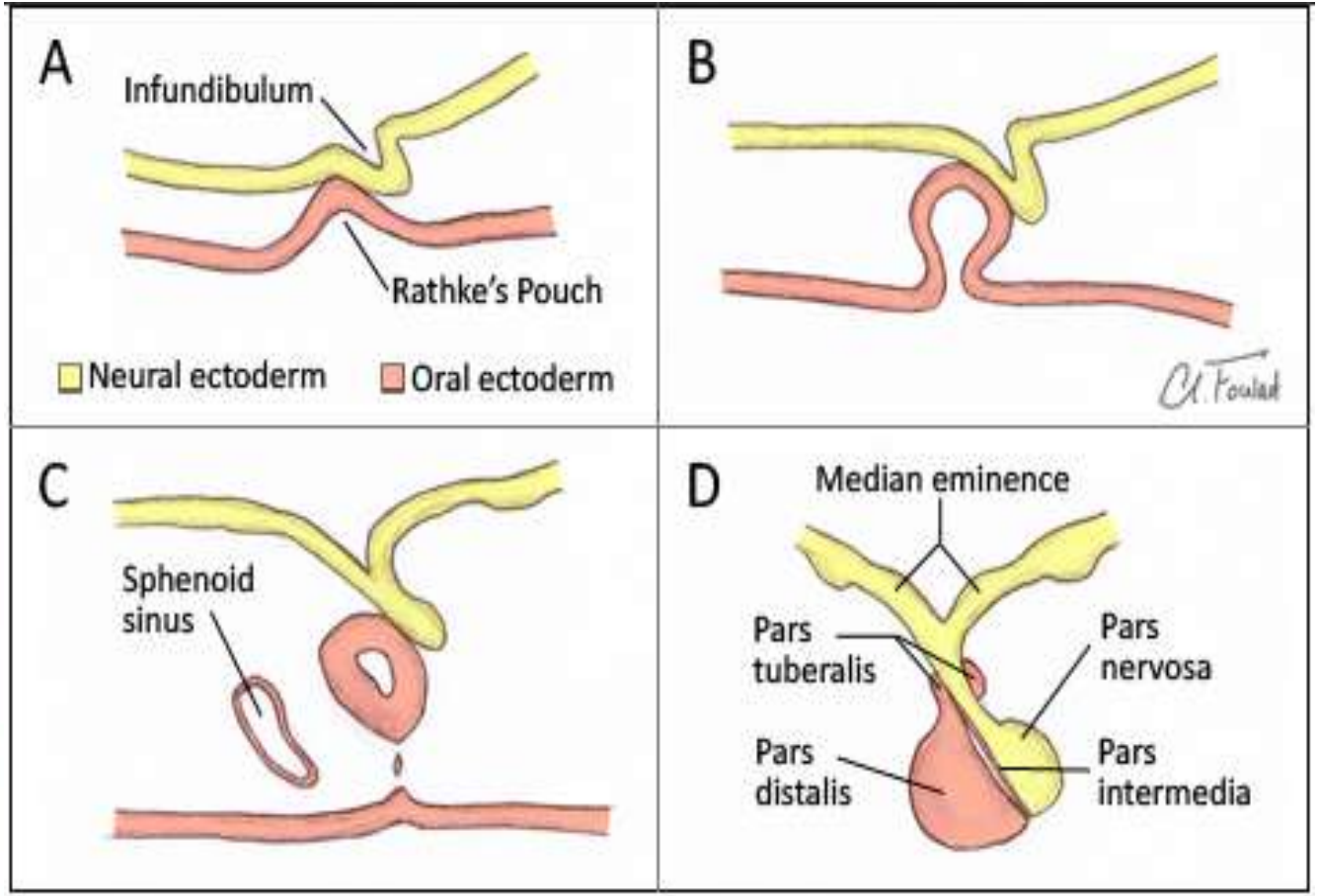
DR UNNIKRISHNAN P
DEPT OF NEUROANAESTHESIA
SCTIMST,TRIVANDRUM,KERALA

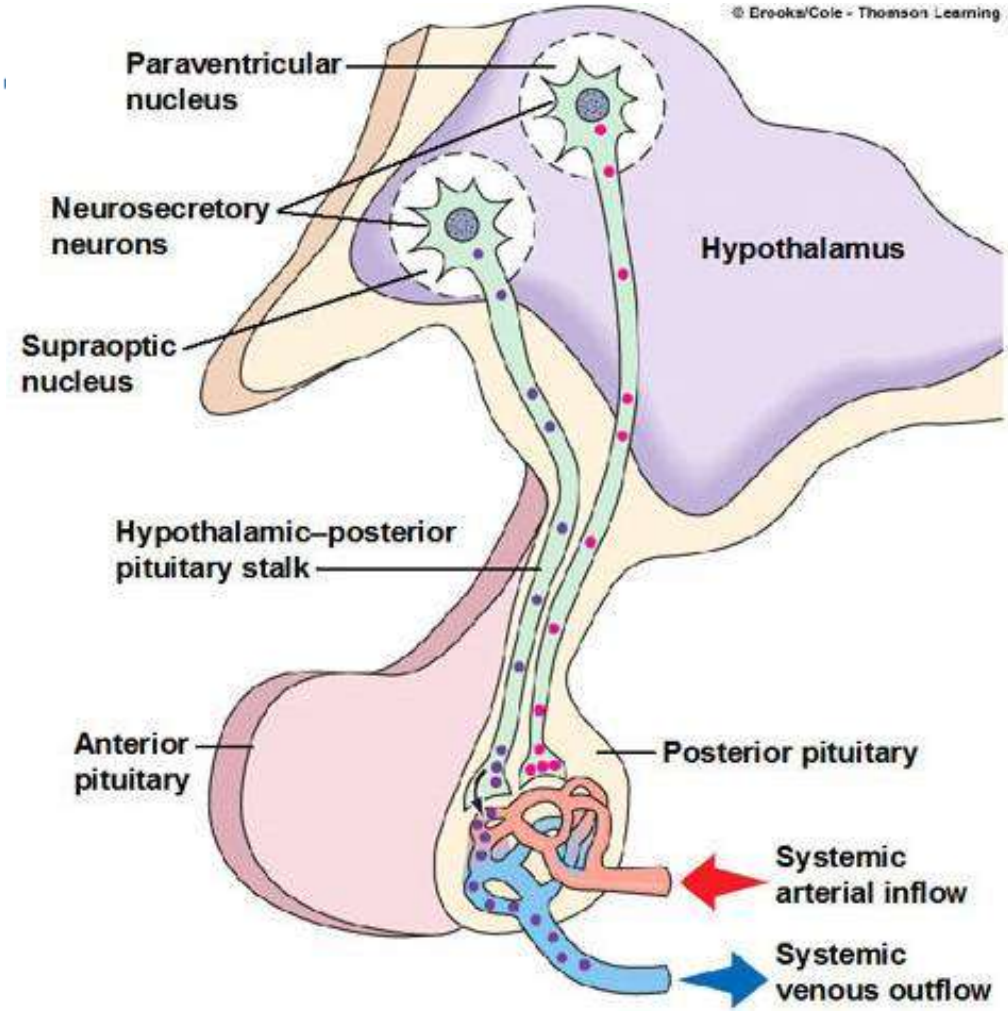
The family

- Hypothalamus…proud mother; has two daughters
- Anterior pituitary [adenohypophysis]…is a gland..having vascular connections with the hypothalamus
- Posterior pituitary [neurohypophysis]…is not a gland but an extension of the

Embryology

- The adenohypophysis develops from Rathke's pouch, which is an upward invagination of oral ectoderm from the roof of the stomodeum
- neurohypophysis develops from the infundibulum, which is a downward extension of neural ectoderm from the floor of the diencephalon


A
Infundibulum
Rathke's Pouch
Neural ectoderm
Oral ectoderm
B
C
Sphenoid sinus
D
Median eminence
Pars tuberalis
Pars nervosa
Pars distalis
Pars intermedia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Paraventricular nucleus
Neurosecretory neurons
Supraoptic nucleus
Hypothalamus
Hypothalamic–posterior pituitary stalk
Anterior pituitary
Posterior pituitary
Systemic arterial inflow
Systemic venous outflow
● = Vasopressin (ADH)
● = Oxytocin

Sherwood

Neurohypophysis

- the supraoptic and paraventricular nuclei of the hypothalamus (cell bodies of the magnocellular, neurosecretory neurons)
- the supraoptico-hypophyseal tract
- the posterior pituitary

Dont injure me… I'll flood your ICU

- Situated in the pituitary fossa limited anteriorly, posteriorly and inferiorly by bony constituents of the sella turcica [a depression in the body of the sphenoid bone]
- Demarcated laterally and superiorly by reflections of dura and elsewhere by the sella turcica

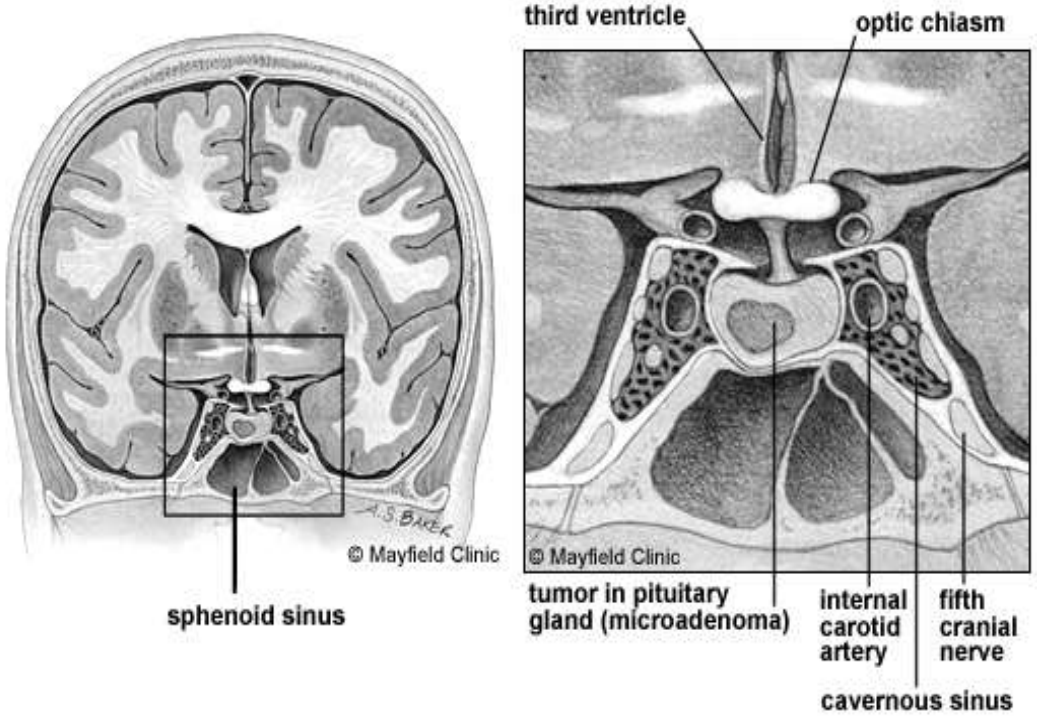
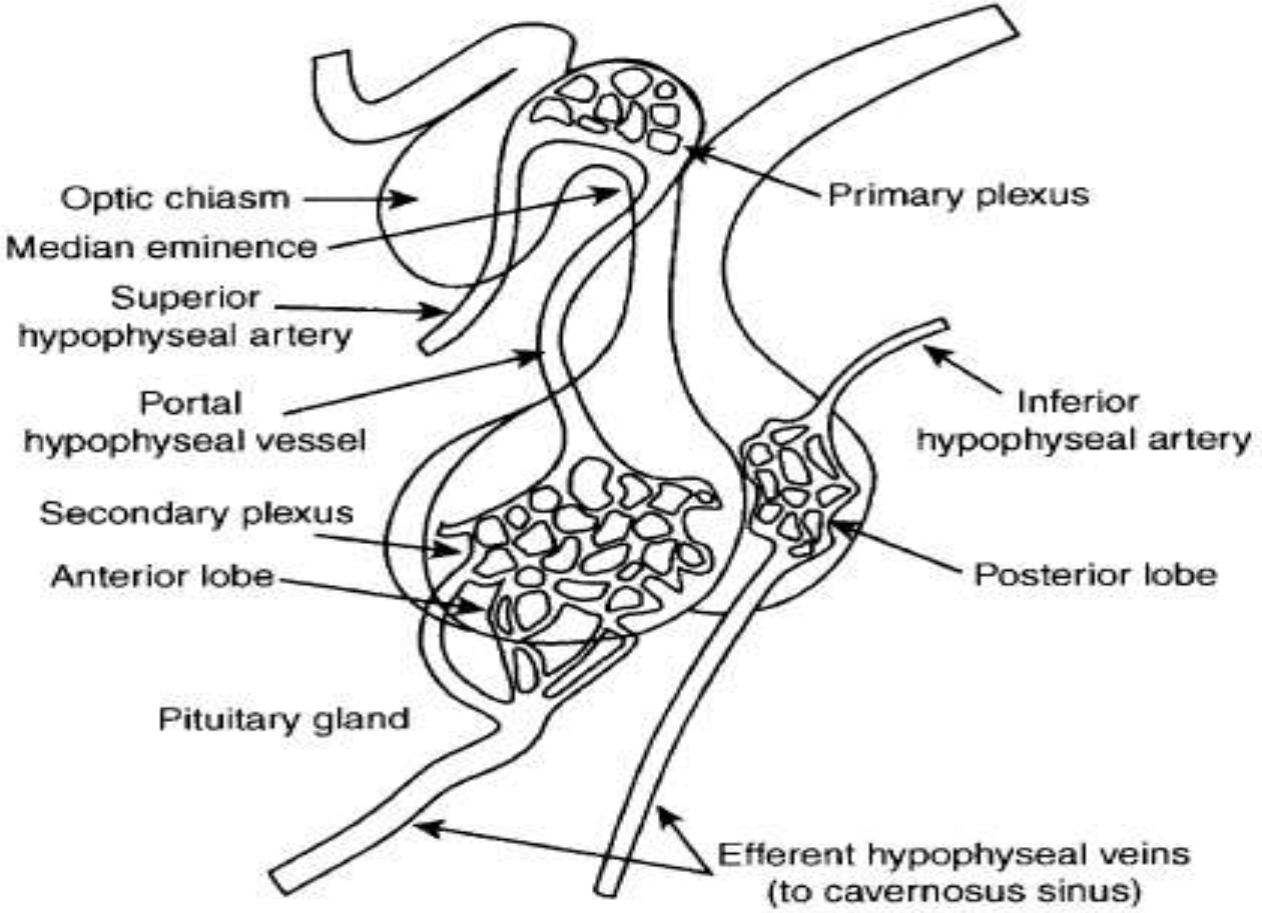


Figure 2: Coronal cross-section of the head at the level of the pituitary gland depicting its relationship to the optic chiasm above, the sphenoid sinus below, and the cavernous sinuses laterally.

Neurohypophysis blood supply

- arterial blood supply from the inferior hypophyseal artery [arises from the meningohypophyseal trunk, a branch of the cavernous segment of the ICA]
- SON and PVN: from the suprahypophyseal, ACOM, PCOM, anterior cerebral and posterior cerebral arteries, all derived from the circle of Willis.
- Venous drainage via the dural, cavernous and


Optic chiasm
Median eminence
Superior hypophyseal artery
Portal hypophyseal vessel
Secondary plexus
Anterior lobe
Pituitary gland
Primary plexus
Inferior hypophyseal artery
Posterior lobe
Efferent hypophyseal veins (to cavernosus sinus)

Vasopressin- 'Neural hormone'

- Synthesis of the VP and OT precursors occurs in the cell bodies of magnocellular neurosecretory neurons within the SON & PVN of the hypothalamus
- They migrate along the axons & get stored in secretory granules within the terminals of the magnocellular neurons in the posterior pituitary

Regulation of vasopressin secretion

Osmoregulation

- The osmoregulatory systems for thirst and VP secretion, and the actions of VP on renal water excretion, maintain plasma osmolality within narrow limits: 284 to 295 mOsmol/kg
- the mean plasma osmolality above which plasma VP increases in response to increases in plasma osmolality ['osmotic threshold' for VP] is 284 mOsmol/kg ; relation is linear usually:[for thirst-281]

Other modes of regulation

- Reductions in circulating volume and hypotension stimulate VP release [baroregulation]
- Nausea and emesis.
- Manipulation of abdominal contents.
- osmoreceptors are situated in anterior circumventricular structures: the subfornicular organ (SFO), and the organum vasculosum of the lamina

How vasopressin ac

	Vasopressin receptor		
	V1a	**V1b**	**V2**
Expression	• Vascular smooth muscle • Liver • Platelets • CNS	Pituitary corticotroph	Basolateral membrane of distal nephron
Amino acid structure	418 amino acids (human)	424 amino acids (human)	370 amino acids (human)
Second messenger system	Gq/11mediated phospholipase C activation: Ca2+, inositol triphosphate & diacyl glycerol mobilization	As V1a	Gïïï€ s mediated adenylate cyclase activation: cAMP production & protein kinase A stimulation
Physiological effects	• Smooth muscle contraction • Stimulation of glycogenolysis. • Enhanced platelet adhesion	Enhanced ACTH release	Increased production & action of aquaporin-2

Receptors

- vasopressin exerts its antidiuretic effect via V_2 receptors and involves insertion of protein water channels called Aquaporins [13 variants]
- vasopressin-responsive water channel in the collecting ducts is aquaporin-2

- NB:AQP1: in apical and basolateral membranes of the PCT and descending loop of Henle facilitates isotonic fluid

Feedback control 24 X 7 !

- Significant changes in secretion occur when osmolality is changed as little as 1%
- Maximum diuresis at plasma VP conc of 0.5 pmol/L or less.
- Maximum urine concentration achieved at plasma VP concentrations of 3-4 pmol/L

Aquaporins do the rest…

- VP stimulates the expression of aquaporin on the luminal surface of the interstitial cells lining the CD.
- Presence of aquaporin (AQP) in the wall of the distal nephron allows resorption of water from the duct lumen along an osmotic gradient, and excretion of concentrated urine.

Mr VP; his other areas of interest

decrease medullary blood flow
stimulate active urea transport in the distal CD
stimulate active Na transport into the renal interstitium

- All these contribute to the generation and maintenance of a hypertonic medullary interstitium, and this augment VP-dependent water resorption.

Diabetes insipidus

- *Diabetes* [Greek] = to go through [describing excessive urination]
- Insipidus [Latin] = without taste

  Mellitus = sweet urine

Diabetes insipidus (DI) involves the passing of urine that is tasteless because of its relatively low sodium content.

Types

- Central --impaired AVP production

- Nephrogenic --due to refractoriness of the distal nephron to the effects of AVP

Causes

Central diabetes insipidus

Congenital: Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy and deafness), familial neurohypophyseal diabetes insipidus

Cranial trauma or brain surgery (especially transsphenoidal surgery)

Brain neoplasms: Craniopharyngioma, germinoma, suprasellar tumors, leukemia, lymphoma, brain metastases

Cerebrovascular disease: Brain infarction, intracranial hemorrhage, aneurysm, Sheehan's syndrome

Brain hypoxia: Cardiac arrest, carbon monoxide poisoning

CNS infections: Meningitis, encephalitis, lues, tuberculosis

Granulomatous infiltration: Sarcoidosis, autoimmune lymphocytic infundibulohypophysitis, Langerhans cell histiocytosis, Wegener's granulomatosis

Causes

Nephrogenic diabetes insipidus

Congenital causes: V2-receptor or aquaporin-2 mutations

Tubulointerstitial renal disease: Sickle-cell disease, polycystic kidney disease, medullary sponge disease, sarcoidosis, obstructive uropathy, renal amyloidosis, Sjögren's syndrome

Hypercalcemia and hypokalemia

Certain drugs: lithium, demeclocycline, amphotericin B, foscarnet, ofloxacin, vinblastine, cidofovir, ifosfamide, orlistat

Incidence

- DI complicates the postoperative course occurs in~ 30% of patients undergoing pituitary surgery,
- transient and relatively benign in the majority of cases
- Chronic postoperative DI : incidence ~ 0.5% to 15% in neurosurgical reviews.
- This is relatively uncommon because >90% of the magnocellular AVP neurons in the SON & PVN must degenerate bilaterally before

Incidence in craniopharyngoma

- Pre-operative central diabetes insipidus has been reported in 8-35% of patients affected with craniopharyngioma, and in 70-90% after surgery.

Pituitary adenoma = adenoma in pituitary; not in Hypothalamus!

- Unusual for pituitary adenomas to present with DI
- They are slow growing also…
- the site of AVP release shifts from the posterior pituitary to the median eminence
- Seen as an upward migration of the posterior bright spot by MRI

Diagnosis of postoperative diabetes insipidus

- **Clinical signs and symptoms**

  Polyuria, high volumes (>2.5 -3.0 mL/kg/hr or 4–18 L/day), with abrupt onset, typically within 24–48 hours postoperatively

- Polydipsia, with craving for cold fluids which better quenches osmotically-stimulated thirst
- With/without hypovolemia, depending on whether the patient has an intact thirst mechanism

- **Laboratory data**

  Dilute urine (specific gravity less than1.005, urine osmolality less than 200 mOsm/kg H2O)

- Normal to increased serum osmolality >295 mOsm/L
- S[Na+] greater or equal to 145 milliequivalent/L with continued diuresis of hypotonic urine
- Irritability or mental status changes, dehydration, shock

Polyuria D.D.s

- osmotic diuresis from glucosuria
  - Is he getting stress doses of steroids?
- Excessive fluids intraoperatively
  - If this large postoperative diuresis is matched with continued intravenous fluid infusions, an incorrect diagnosis of DI may be made based on the resulting hypotonic polyuria; *medullary washout* phenomenon
- diuretic use (including mannitol)
- the recovery phase of acute renal failure
- primary polydipsia, and
- after relief of obstructive uropathy.

Act carefully…..

- Therefore, if the serum [Na+] is not elevated concomitantly with the polyuria, the rate of parenterally administered fluid should be slowed with careful monitoring of the serum [Na+] and urine output until a diagnosis of DI can be confirmed by continued hypotonic polyuria in the presence of hypernatremia or hyperosmolality

Water Deprivation Test

withhold water:
Mild dehydration

rise in plasma Na

stimulates AVP production

water conservation

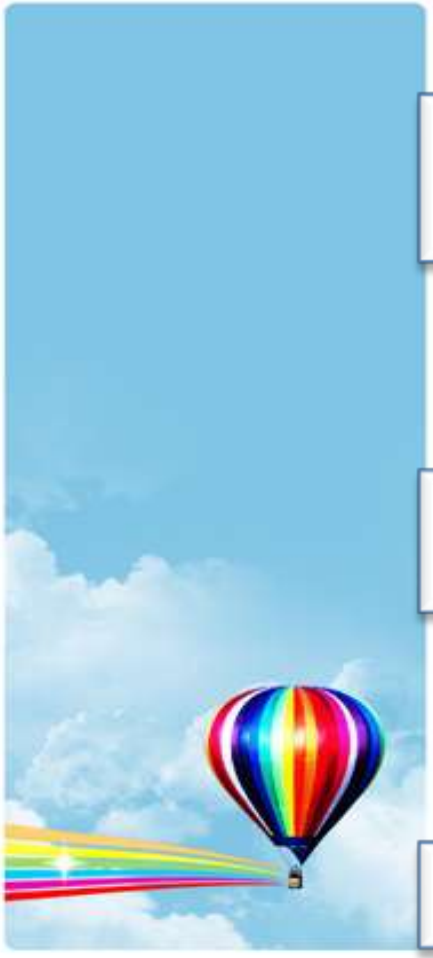
urine output, should ↓, and urine osmolality, which should ↑

Water Deprivation Test

- dangerous in ICU patients
- can induce hypovolemia and hemodynamic instability.
- Further, ICU patients with DI often have already developed at least mild hypernatremia spontaneously, which obviates the rationale
- ‘inappropriately low urine osmolality in the face of even very mild hypernatremia’:

g

- Normal response to hypernatremia: Urine osmolality >800 mOsmol/kg H2O
- Response in partial DI: Urine osmolality 300–700 mOsmol/kg H2O
- Response in complete DI: urine osmolality <300 mOsmol/kg H2O



Differentiation of central and nephrogenic DI

- can be made by measuring plasma AVP levels after water deprivation or spontaneous development of mild hypernatremia

- Normal response to hypernatremia:Plasma AVP concentration >2 pg/mL
- Response in partial DI: Plasma AVP concentration may reach 1.5 pg/mL
- Response in complete DI: Plasma AVP concentration undetectable
- Response in nephrogenic DI: Plasma AVP concentration can exceed 5 pg/mL

Differentiation of central and nephrogenic DI

- More commonly achieved by assessing urine osmolality before and after a single dose of aqueous AVP (5 units subcutaneously) or the AVP analog desmopressin (1 or 2 µg subcutaneously or IV)

- The response in central DI may be blunted if there has been down-regulation of aquaporin channels or a significant degree of medullary washout

- Normal response: No more than a 5% increase in urine osmolality
- Response in partial central DI: 10–50% increase in urine osmolality
- Response in complete central DI: At least a 50% increase in urine osmolality
- Response in nephrogenic DI: No change in urine osmolality is expected

MRI in DI

- Bright spot in the sella can be visualized on T1-weighted images when stored vasopressin and oxytocin are present in neurosecretory granules of the posterior pituitary.Absence of this bright spot is characteristic of DI
- Not very reliable

MRI in DI

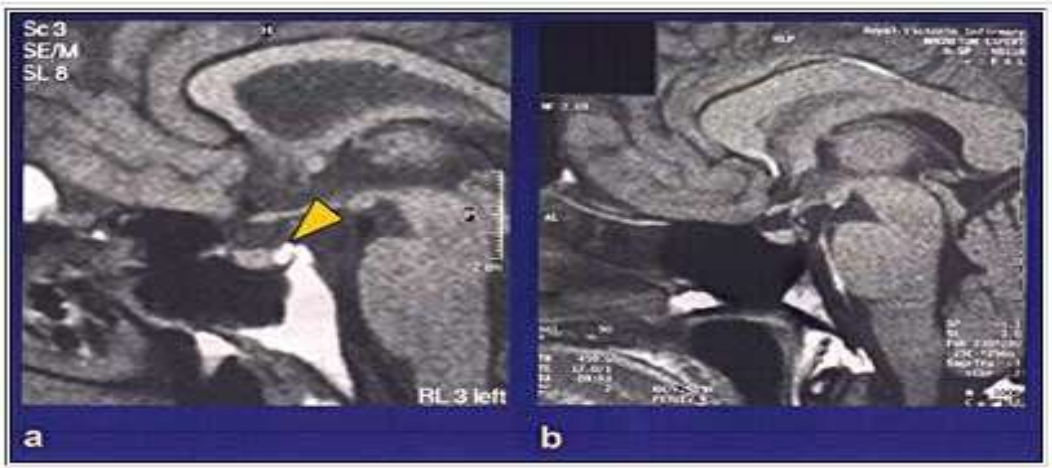


Figure 11. Loss of the posterior pituitary 'bright spot' on T1 weighted MRI in hypothalamic diabetes insipidus. The normal posterior pituitary can be demonstrated as a 'bright spot' within the sella turcica on T1-weighted MRI (a). This increased signal intensity can be lost in HDI (b). An ectopic posterior pituitary 'bright-spot' can be seen some cases of childhood onset hypopituitarism, implying failure to complete normal developmental migration. Function can be normal despite the aberrant position

Variations in Clinical Course

- classic studies of pituitary stalk transection describes three types: transient, permanent, or triphasic
- **Transient DI** :begins within 24 to 48 hours of surgery and usually abates within several days
- **Permanent**

Transient DI

- severing of the neuronal connections or axonal shock from perturbations in the vascular supply to the pituitary stalk
- temporary dysfunction of AVP producing neurons
- resolves as the vasopressinergic neurons regain full function.

Permanent DI

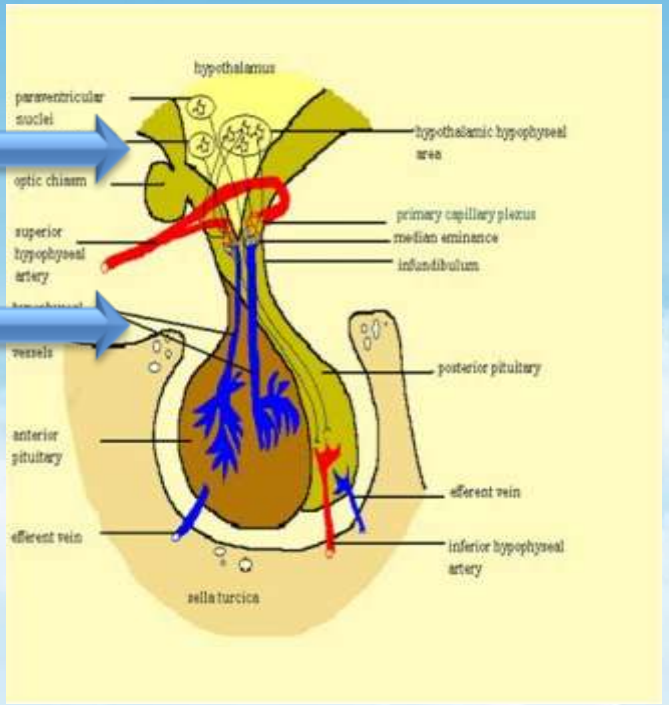
- Rarely persistent DI may follow as preformed stores of AVP are depleted and no additional AVP is synthesized.

Permanent DI

- In a series of 24 patients*…

80% to 100% DI with higher stalk injury

low pituitary stalk section at the level of the diaphragm sella, only 62% developed permanent DI



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*Sharkey PC, Perry JH, Ehni G. Maclean JP, West CD, et al

Triphasic DI

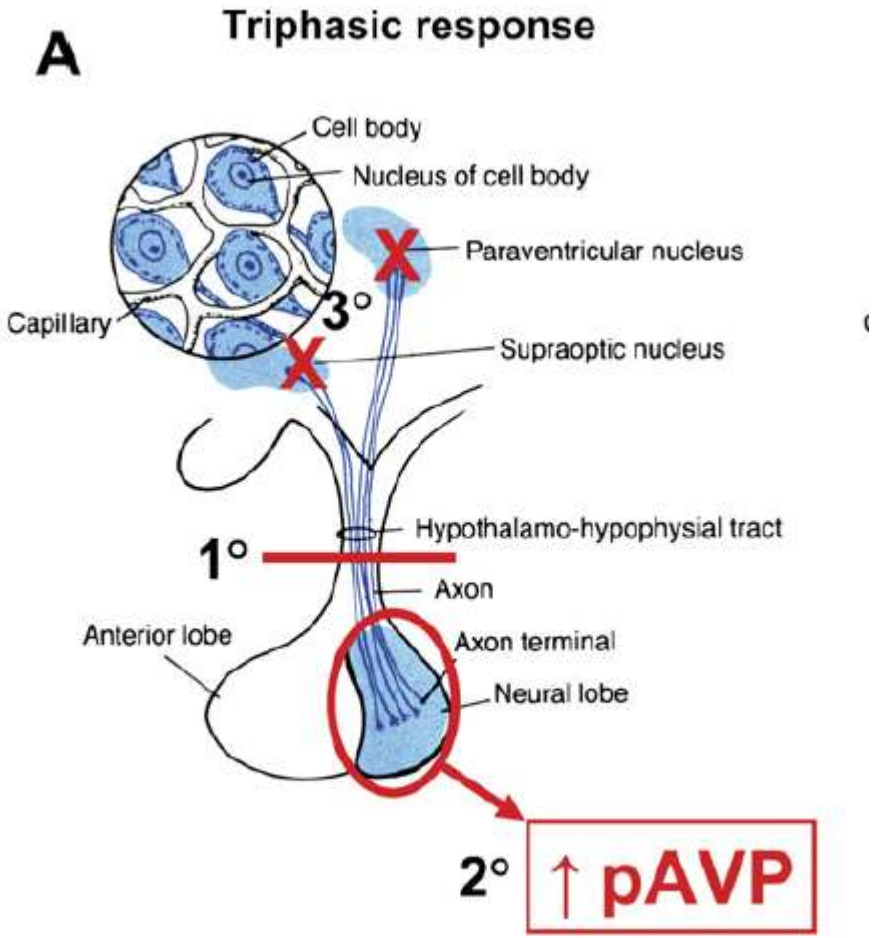
- First phase of DI typically lasts 5 to 7 days
- transitions into a second antidiuretic phase of SIADH
- caused by the uncontrolled release of AVP from degenerating posterior pituitary tissue, or from the remaining magnocellular neurons whose axons have been severed

Triphasic DI

- Urine quickly becomes concentrated in response to the elevated plasma AVP levels and urine output markedly decreases.
- Continued administration of excess water during this period can quickly lead to hyponatremia and hypoosmolality. can last from 2 to 14 days .

Triphasic DI

- After the AVP stores are depleted from the degenerating posterior pituitary, the third phase of chronic DI then typically ensues, although not always
- In this phase, there are insufficient remaining AVP neurons capable of synthesizing additional AVP, thereby resulting in permanent DI


A
Triphasic response
Cell body
Nucleus of cell body
Paraventricular nucleus
3°
Capillary
Supraoptic nucleus
Hypothalamo-hypophysial tract
1°
Axon
Anterior lobe
Axon terminal
Neural lobe
2°
↑ pAVP

Complications

profound hypernatremia,hyperosmolality, and dehydration, If sufficient water intake or hypotonic IV fluid is not provided

- unlikely if the total body water deficit is entirely due to electrolyte free water loss; very likely with even small degrees of co-existing total body sodium depletion

Hypokalemia, hypomagnesemia, and hypophosphatemia

- Also should be anticipated

TREATMENT

‘Expectant’ monitoring

Close monitoring of water balance (fluid intake and output) Urine osmolality or specific gravity every 4 to 6 hrs, until resolution or stabilization

Frequent serial measurements of serum Na,K,Mg, and P concentration. Serum [Na+] every 4 to 6 hours, until resolution or stabilization

Appropriate titration of IV fluids to prevent or correct volume depletion and hypernatremia

Confirm DI first…

- Avoid other causes of polyuria
- DI = continued hypotonic polyuria despite hyperosmolality.
- criteria for subsequent redosing of ADH analogues need not be as stringent, and can be based simply on the redevelopment of polyuria

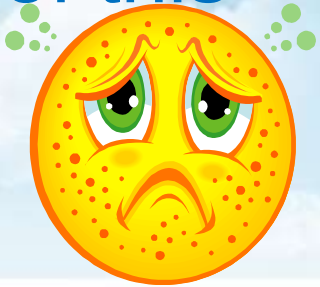
Maintenance of fluid balance

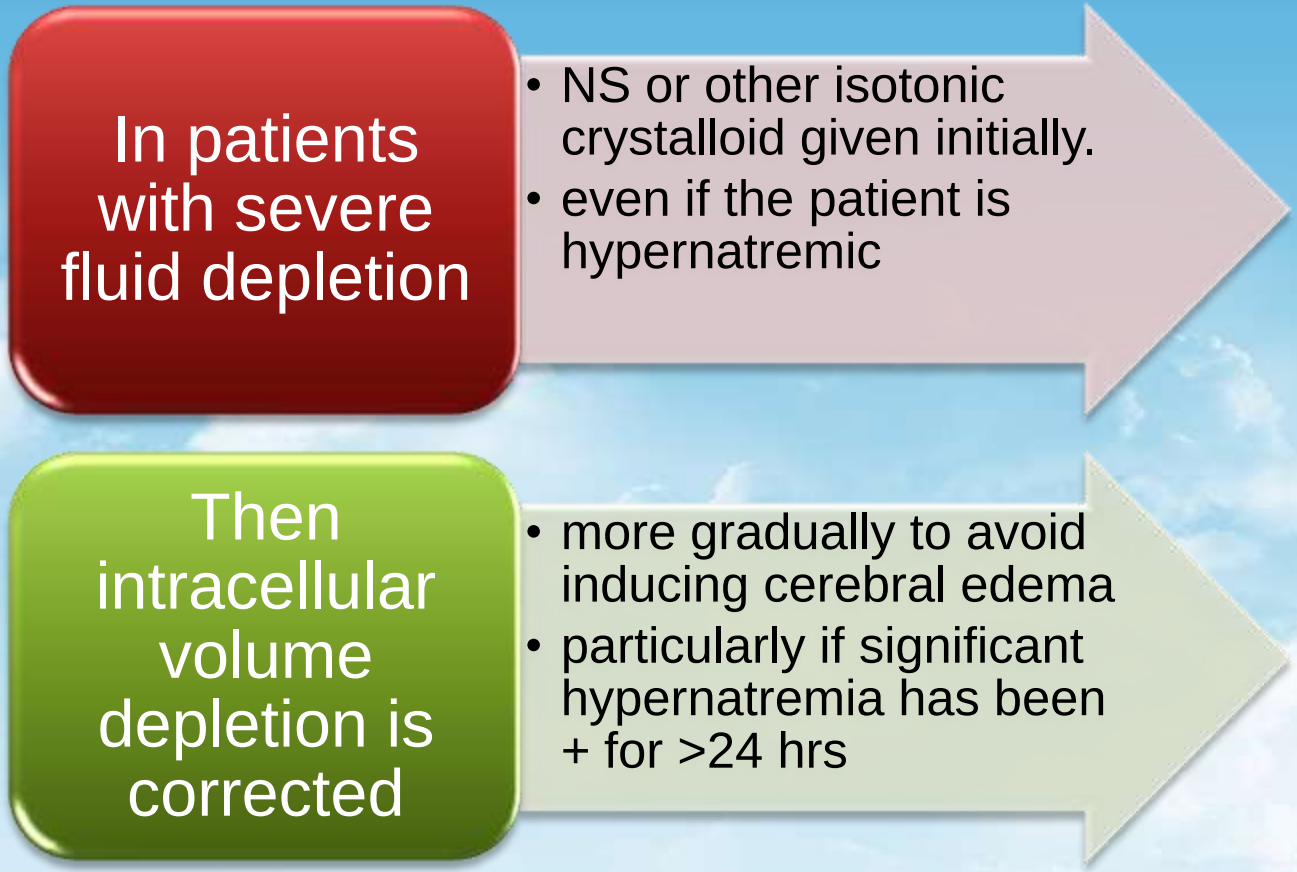
- Allow patient to drink according to thirst
- Supplement hypotonic intravenous fluids (D5W to D5 1/2NSS) if patient is unable to maintain a normal plasma osmolality and serum [Na+] through drinkin

Maintenance of fluid balance

- The established water deficit = 0.6 X premorbid weight X [1-140/serum Na (mmol/L)]

- Ongoing losses decrease the efficacy of this formula




In patients with severe fluid depletion
• NS or other isotonic crystalloid given initially.
• even if the patient is hypernatremic
Then intracellular volume depletion is corrected
• more gradually to avoid inducing cerebral edema
• particularly if significant hypernatremia has been + for >24 hrs

Maintenance of fluid balance

- even slow correction of the volume deficit may necessitate a high rate of hypotonic fluid administration if there is ongoing polyuria.

- Overhydration →water diuresis →medullary washout→sustaining the polyuria even if the DI resolves.

Monitor for resolution of transient DI or triphasic response

- Positive daily fluid balance >2 L suggests possibility of inappropriate antidiuresis

- If so antidiuretic hormone therapy should be held and fluids restricted to maintain serum [Na+] within normal ranges

Manage anterior pituitary insufficiency

- Any patient with postoperative DI, and particularly those manifesting a triphasic response, should be assumed to have anterior pituitary insufficiency
- Cover with stress dose corticosteroids (hydrocortisone 100 mg iv every 8 hours, tapered to 15mg to 30mg by mouth daily) until anterior pituitary function can be

Desmopressin

Aqueous AVP;why this desmo get more attention than me ?!^%

- Aqueous AVP has a half-life of 2–4 hours and can be given s/c, im,IV bolus, or by continuous IV infusion. It is a potent vasoconstrictor,owing to its effect on vascular V1 receptors
- Dose 4-10 units s/c or i.m. repeated every 4 to 6 hours
- recommended only for diagnostic purposes or in acute conditions (e.g., trauma) in which the DI might be transient

Preparations

PITRESSIN TANNATE	• 5u / mL im • Q4-8H
SYNTHETIC LYSINE VASOPRESSIN	• 50 u / mL in isotonic saline • DRODID nasal spray
DESMOPRESSIN	• 1-2µg bd iv or s/c • 10-20 µg bd/tid nasal spray • 200-600 µg bd / tid orally

Desmopressin;I ‘ve only one friend… V2

- 1-deamino-8-D-arginine-vasopressin
- Desmopressin, initial dose of 1 µg to 2 µg i.v. or s/c dosed at 1–2 µg every 8–12 hours; half-life

INTRANASAL SOLUTION	100 UG/ML
INTRANASAL SPRAY	10 UG/SPRAY
IM	4 UG/ML
ORAL	200UG TAB

- <2 yr: 2-5ug intranasal; >2 y:5-10 ugrams/day
- onset 15 min after ini, 60 min after oral

Antidiuretic hormone therapy

- Parenteral routes are preferable, because this obviates any concern about absorption, causes no significant pressor effects, and has the same total duration of action as the other routes
- Redose when urine output 200 mL to 250 mL per hour for greater than or equal to 2 hours, with urine specific gravity less than 1.005 or urine osmolality less than 200 mOsm/kg H2O

Desmopressin : patiently watch my response….

- Prompt reduction in urine output and the duration of antidiuresis is approximately 6 to 12 hours.
- Each dose of desmopressin should be given after the recurrence of polyuria, but before the patient actually becomes hyperosmolar *to avoid fluid retention and hyponatremia*

Repeat the dose…..when?

- Excretion of 200 mL to 250 mL per hour of urine with an osmolality less than 200 mOsm/kg H_2O or specific gravity less than 1.005 affirms the need for retreatment with desmopressin

I hate this fixed dose schedule…. Give on demand….

- Dosing desmopressin on an as needed basis, also has the benefit of
- allowing the detection of return of endogenous AVP secretion
- or the start of the second phase of a triphasic response,
- by a lack of return of polyuria after the effects of the previous desmopressin dose have dissipated

Desmopressin in c/c DI

- intranasal or oral desmopressin.
- The nasal spray delivers metered single doses of 0.1 mL (10 micrograms).The reliability diminished in patients with mucosal atrophy, nasal congestion, scarring, or nasal discharge
- So wait until several days postoperatively before using intranasal desmopressin, especially in patients who have nasal packing in place.

Intranasal Desmopressin in c/c DI

- Duration 6 to12 hours: most patients require twice daily dosing.
- It is often useful to permit intermittent polyuric episodes every 1 to 2 weeks by delaying a dose of desmopressin, thereby verifying continued presence of DI and allowing any retained excess water to be excreted so that normal water balance is maintained.

Dont always eat through nose!

- Patients with chronic rhinitis or mucosal scarring: oral preparations more viable option
- available in 0.1 mg to 0.2 mg dosing options
- 20 times higher dose than intranasal spray as >99% of the oral dose is destroyed by gastrointestinal peptidases.
- central DI : on average 200 mg to 600 mg of oral desmopressin two times per day to control polyuria
- should be taken on an empty stomach to

Desmopressin : side effects

- headache, nausea, nasal congestion,flushing and abdominal cramping
- no pressor effects because it selectively binds to the AVP V2 receptors
- safe in patients with coronary or hypertensive cardiovascular disease

Patient with DI coming for surgery

- just before surgery→usual dose intra nasally or aq.vasopressin 100 mu iv bolus f/b constant infusion of 100-200 mu/hr [0.1mU/kg/hr]
- isotonic ivfs
- p.osmolarity hourly..closely monitor Na
- if >290 mosm/l → hypotonic ivfs & increase vasopressin infusion >200 mu/ hr

Treatment of Nephrogenic DI

- Stopping any causative drugs
- Monitoring fluid balance and electrolyte levels, Supplying IVFs
- restricting Na intake

Treatment of Nephrogenic DI

Na restriction and thiazides
→ mild volume contraction

stimulates sodium and water reabsorption in the PCT

decreases water delivery to the distal nephron→ limit polyuria

Treatment of Nephrogenic DI

Amiloride +/- thiazide

- Especially when Li exposure is the cause
- amiloride limits lithium entry into tubular cells

Others

- Indomethacin and ibuprofen
- Desmopressin;in those with receptor mutations high doses may be useful

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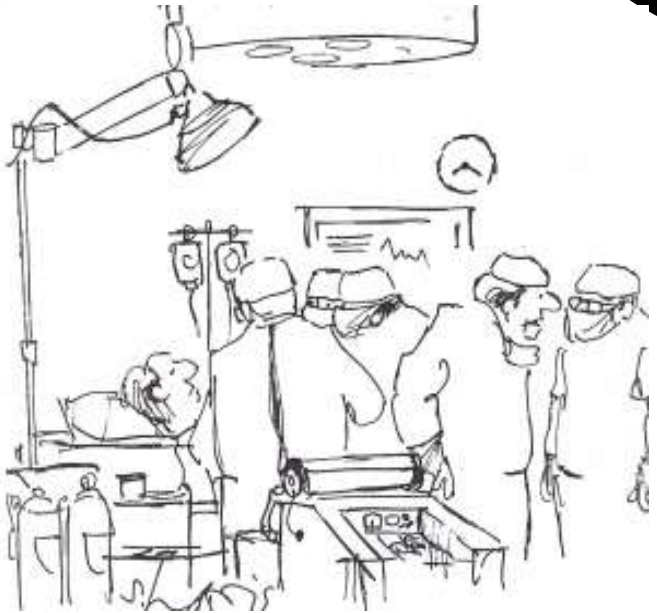

'We'll just mill around
till he's asleep, and then
send him back up.
This operation is
actually for a placebo effect.'

Thank You