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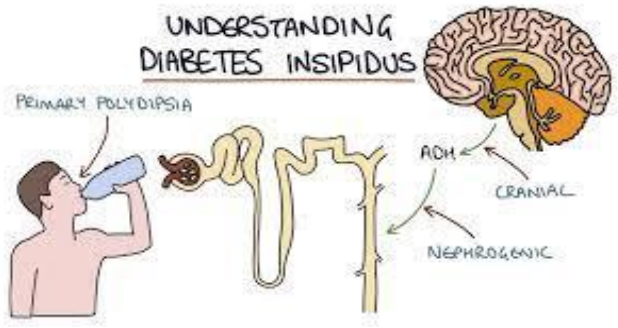

Diagnosis & Management of diabetes insipidus in children

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Introduction

- Regulation of water intake and excretion helps maintain extracellular fluid tonicity, within a narrow range, which is crucial for proper cell functions.

Introduction

- Maintenance of water balance is primarily dependent on :

➢ Intact thirst mechanism

➢ Vasopressin synthesis

➢ Renal tubular responsiveness to vasopressin

Introduction

- Diabetes insipidus (DI) is a heterogeneous clinical syndrome of disturbance in water balance characterized by the passage of large volumes of dilute urine and the presence of an inordinate thirst.

(polydypsia and polyuria)

Introduction

- In children three pathophysiologic mechanisms give rise to polydipsia (hypotonic) and polyuria:

➢ Central DI : defective vasopressin synthesis and/or secretion.

➢ Nephrogenic DI : defective renal tubular response to vasopressin action.

➢ Primary polydypsia due to compulsive water drinking (psychogenic) or defective thirst mechanism (dipsogenic).

Diagnosing polyuria-polydipsia syndrome

- Diagnosing is essential for making the optimal treatment decision.
- Diagnosing any suspected case of DI usually involves the following steps:
- 1. Confirmation of hypotonic polyuria
- 2. Diagnosis of the type of polyuria-polydipsia syndrome
- 3. Identification of the underlying etiology

1- Confirmation of hypotonic polyuria

- Polyuria is characterized by a urine volume in excess of :

✓2 l/m 2 /24 h

✓150 ml/kg/24 h at birth

✓100–110 ml/kg/24 h until the age of 2 years

✓40–50 ml/kg/24 h in the older child and adult

✓ > 4 ml/kg/hr in children

✓ > 6 ml/kg/hr in neonates

1- Confirmation of hypotonic polyuria

- Presence of polyuria :

✓Measurement 24 hours urine output (minimized by obtaining an 8 h)

✓Measurement fluid intake

✓Weighing the diaper

1- Confirmation of hypotonic polyuria

- Once polyuria is established :

✓Urine osmolality > 800 mOsmol/kg (solute diuresis VS water diuresis)

Solute diuresis :

- Glucosuria
- Sodium-glucose co-transporter 2 inhibitor (200 mL over six hours after a 25 mg dose of empagliflozin)
- Exogenous urea
- Glucocorticoids
- Very high protein diet
- Saline
- Bilateral urinary tract obstruction
- Mannitol

Solute diuresis

If unsure, despite the history and initial laboratory testing :

- Total daily osmolar output (>1000 mosmol)

Total daily osmolar output = Urine osmolality x 24-hour urine volume

1- Confirmation of hypotonic polyuria

- As an alternative to urine osmolality, urine SG is also useful in identifying a hypotonic polyuric disorder.
- The SG value depends on the number and the size of particles in the urine, unlike urine osmolality which solely depends on the number of particles in the urine.

1- Confirmation of hypotonic polyuria

- Although urine SG and urine osmolality generally correlate well, presence of large molecules might elevate urine SG despite the chance of the urine osmolality actually being low.
- Unlike falsely elevated urine specific gravity, false low values of urine specific gravity are uncommon and a low urine specific gravity suggests DI or primary polydipsia.

2-Diagnosis of the type of polyuria-polydipsia syndrome

Initial tests :

➢Urine osmolality < 300 mOsmol/kg :

- High serum sodium (>146 mmol/L) : DI .
- High plasma osmolality (≥300 mOsm/Kg) : DI.

- Low normal or low sodium (<135 mmol/L) : primary polydipsia.
- Low plasma osmolality (≤280 mOsm/Kg) : primary polydipsia.

2-Diagnosis of the type of polyuria-polydipsia syndrome

- *Where the initial diagnostic testing is indeterminate*

➢ Normal serum sodium/plasma osmolality

➢ Urine osmolality value of 300 – 800 mOsm/Kg

- *Central DI vs. nephrogenic DI*

Further testing must be considered

2-Diagnosis of the type of polyuria-polydipsia syndrome

Other tests :

A : Water Deprivation Test

B : Measurement of Plasma AVP

C : Measurement of Plasma Copeptin

D : Hypertonic Saline Infusion Test

E : Arginine Plus Copeptin

A : Water Deprivation Test

- The normal physiologic response to the water restriction test :

➢ Once the plasma osmolality reaches 295 to 300 mosmol/kg (normal 275 to 290 mosmol/kg) or the plasma sodium is 145 mEq/L or higher, the effect of endogenous ADH on the kidney is maximal.

➢ At this point, administering desmopressin or vasopressin will not further elevate the urine osmolality .

Water Deprivation Test
TESTING PROTOCOL

- Any electrolyte abnormalities (potassium, calcium) must be corrected prior to the test.
- The patient has to discontinue any medications that can affect urine output (diuretics, SGLT-2 inhibitors, desmopressin, carbamazepine, chlorpropamide, glucocorticoids, NSAIDS) 24 hours prior to initiation of dehydration.
- Refrain from activities such as smoking and caffeine intake that might affect AVP release or urine output.

Water Deprivation Test
TESTING PROTOCOL

- ✓If suspected adrenal insufficiency give hydrocortisone 4 hours prior to test as cortisol is required for excretion for water.
- ✓Thyroid and adrenal reserve must be normal or adequately replaced.

Water Deprivation Test
TESTING PROTOCOL

Stop all fluid intake

- Most patients with a urine osmolality >100 mosmol/kg can safely undergo overnight fluid restriction and be evaluated the following morning.
- By contrast, individuals with severe polyuria and a urine osmolality <100 mosmol/kg should **not** undergo overnight water restriction. Rather, they should refrain from fluids for two to three hours prior to evaluation.

Water Deprivation Test
TESTING PROTOCOL

- The test is performed after breakfast.
- It is started after the child voids or, in infants, after the first spontaneous void after the morning feed.
- Body weight and plasma sodium and osmolality are measured after the patient voids.
- No further fluid is given until the test is terminated.

Water Deprivation Test
TESTING PROTOCOL

- Record each urine void and measure the urine volume and urine osmolality.
- Weight and vital signs are obtained every two hours for the first four hours and then hourly.
- The plasma sodium and osmolality are measured at four hours and then every two hours until the conclusion of the test.

Water Deprivation Test
TESTING PROTOCOL

- The test is terminated when one of the following end points are attained:

✓Urine osmolality is ≥800 mosmol/kg. (SG ≥1.020)

✓Plasma osmolality exceeds 295 or 300 mosmol/kg or plasma sodium is 145 mEq/L or higher.

✓The patient has lost 5 percent of body weight or exhibits signs of volume depletion.

✓If the period of water restriction reaches 6 h in infants less than six months of age, 8 h in children from six months to two years of age, or 12 hours in children older than two years of age.

Water Deprivation Test
TESTING PROTOCOL

- The duration of water restriction :

Hours of projected water restriction = Weight (kg) x (0.03) x 1000 (mL) ÷ Measured urine volume/hour (mL/hour)

Water Deprivation Test
TESTING PROTOCOL

- At the end of the test, weight, vital signs, plasma sodium, plasma osmolality, and urine osmolality should be measured.
- A specimen should also be obtained for measurement of plasma ADH.

Water Deprivation Test
TESTING PROTOCOL

- 1- Children with impaired urinary concentration despite plasma osmolality of 295 mosmol/kg or a plasma sodium of 145 mEq/L
- 2- Children who lose 5% or more of their body weight
- 3- Test is terminated due to time

Desmopressin is administered

(5 to 10 mcg by nasal insufflation or 2 to 4 mcg IV or SC)

Water Deprivation Test
TESTING PROTOCOL

- The urine volume and osmolality are then measured every 30 minutes for two hours to detect any antidiuretic response.
- The two-hour monitoring period is particularly important if there is dilatation of the urinary bladder by previous high urine volumes. (dilution with post-micturitional residual urine)
- Allow the child to drink but not excessively. Fluid intake should be no more than twice the volume of urine passed during fluid restriction.

INTERPRETATION OF RESULTS

- In normal individuals, with dehydration, the urine osmolality usually increases up to 800 – 1200 mOsm/Kg .

INTERPRETATION OF RESULTS

- Urine osmolality <300 mOsm/Kg with a concomitant plasma osmolality >300 mOsm/Kg or a sodium level >146 mmol/L is suggestive of either complete CDI or complete NDI.

❖After desmopressin administration :

- Increase at least **>50%** in urine osmolality suggests complete CDI
- No or minimal elevation (<15 percent) in urine osmolality suggests complete NDI.

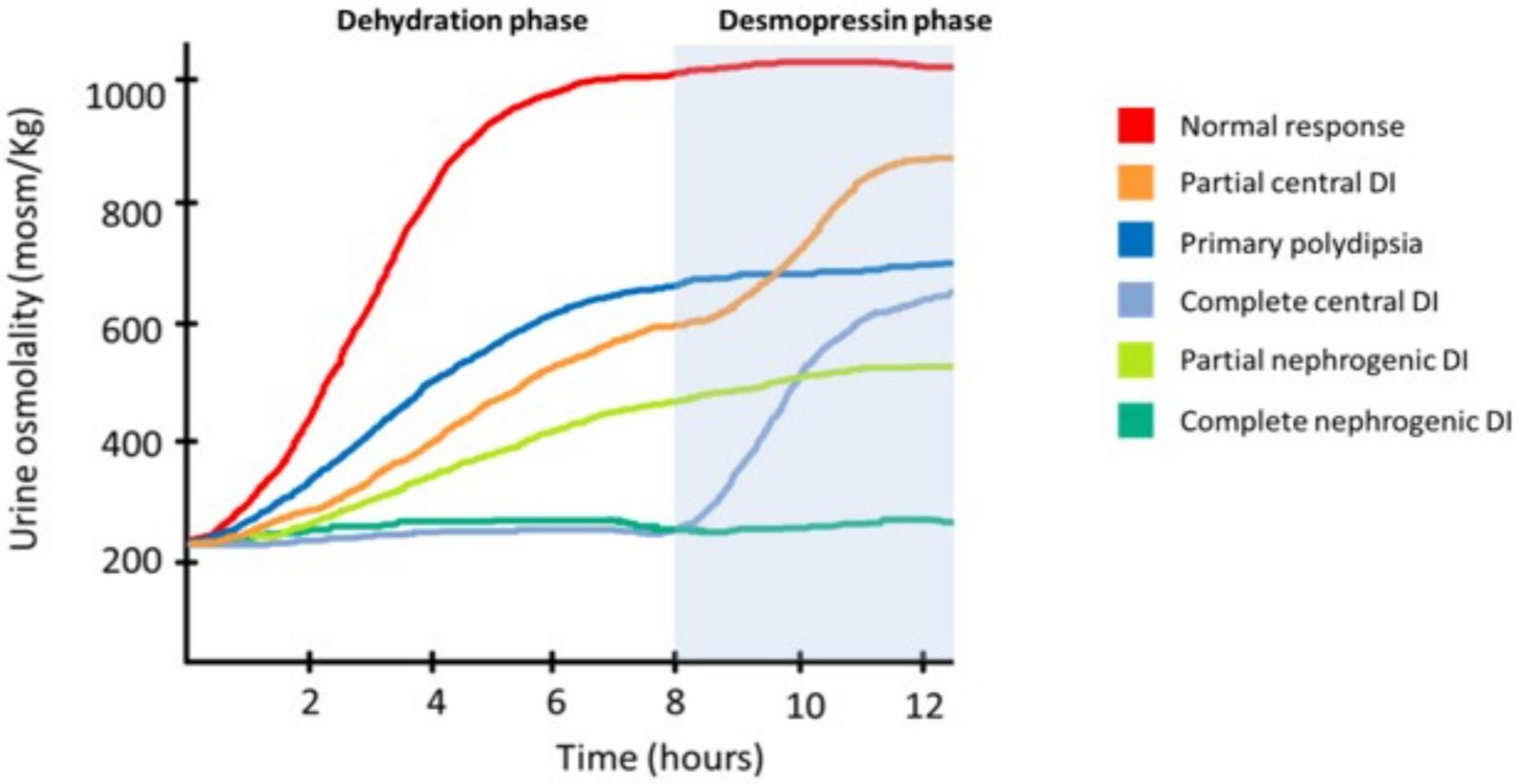
INTERPRETATION OF RESULTS

- In patients with partial DI (central or nephrogenic) the urine osmolality after water deprivation is usually between 300 – 800 mOsm/Kg and there can be <50% increase in urine osmolality following desmopressin administration.

INTERPRETATION OF RESULTS

- In primary polydipsia, water deprivation results in an increase in urine osmolality, between 300 – 800 mOsm/Kg (usually up to 600 – 700 mOsm/Kg), without a substantial increase in plasma osmolality.
- Following desmopressin administration, an increase of <9% in urine osmolality is associated with primary polydipsia .

Graphical representation of the water deprivation test



LIMITATIONS

- Long standing central DI, due to chronic deficiency of AVP, the aquaporin-2 channels are down-regulated as AVP is required for the synthesis and membrane translocation of these channels .
- Therefore, administration of desmopressin after water deprivation might not result in an adequate increase in urine osmolality, which could misleadingly suggest a picture of nephrogenic DI.

LIMITATIONS

- Chronic primary polydipsia can suppress the release of endogenous AVP due to increased intravascular volume and decreased plasma osmolality from high volumes of water intake.
- In this situation, water deprivation might not lead to an adequate rise in plasma osmolality high enough to stimulate the release of endogenous AVP.
- This can result in a sub-optimal increase in urine osmolality, thus simulating a clinical picture of central/nephrogenic DI.

LIMITATIONS

- Test should not be performed in infants.

B : Measurement of Plasma AVP

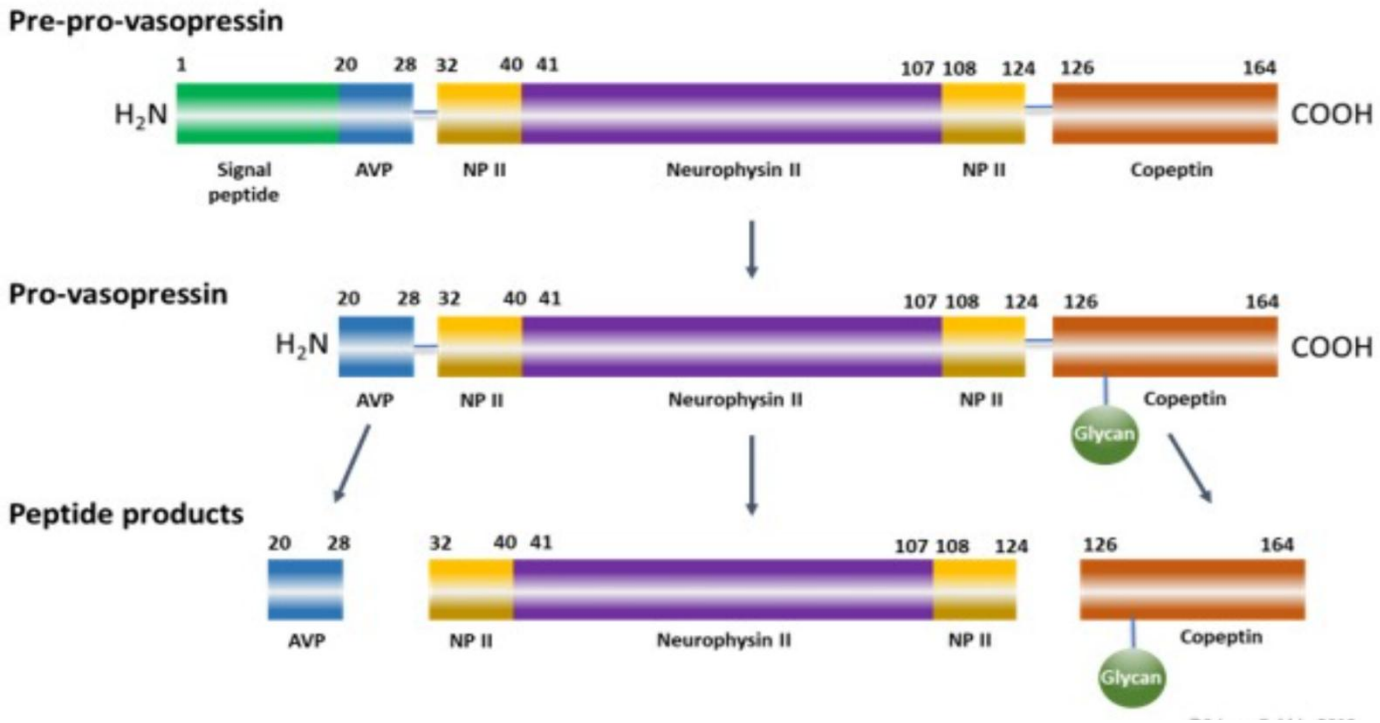
- In NDI, the plasma AVP levels is high. (≥3 pg/ml)
- In CDI, plasma AVP is low . (< 1.8 pg/ml)
- In primary polydipsia, plasma AVP is normal .

LIMITATIONS

- AVP is rapidly cleared from the plasma, with a half-life of around 16 minutes.
- Large amount of circulating AVP is bound to platelets and failure to adequately segregate platelets from the plasma after blood sampling or prolonged storage of unprocessed blood samples can lead to wide fluctuations or even an increase in the measured plasma AVP levels.

C : Measurement of Plasma Copeptin

- Copeptin is the C-terminal peptide of pro-vasopressin that is co-secreted with AVP in stoichiometric amounts from the posterior pituitary.



C . Measurement of Plasma Copeptin

- Plasma levels of copeptin strongly correlate with plasma AVP levels.
- Plasma copeptin demonstrates the same response to changes in plasma osmolality and plasma volume as does plasma AVP.
- Copeptin can remain stable for days after sampling of blood.

(7 days at room temperature and at 14 days at 4°C)

C : Measurement of Plasma Copeptin

- Baseline plasma copeptin of ≥21.4 pmol/L NDI (partial and complete)
- Baseline plasma copeptin of < 2.6 pmol/L complete CDI

- Baseline plasma copeptin of ≥ 2.6 pmol/L :

hypertonic saline infusion

- Plasma copeptin levels of ≥ 4.9 pmol/L primary polydipsia
- Plasma copeptin levels of < 4.9 pmol/L CDI (partial or complete)

C : Measurement of Plasma Copeptin

- the ratio of Δ copeptin from start till the completion of water deprivation to the serum sodium at the end of water deprivation test has been shown to discern :

➢ partial central DI (<0.02 pmol/L)

➢ primary polydipsia (≥0.02 pmol/L)

C : Measurement of Plasma Copeptin

- Plasma copeptin as a valuable marker to predict post-operative risk for DI after pituitary surgeries:

➢ plasma levels of <2.5 pmol/L predicting the risk of DI with a positive predictive value of 81% .

➢ plasma levels of >30 pmol/L on postoperative day 1 demonstrating a negative predictive value of 95% to rule out DI.

D : Hypertonic Saline Infusion Test

- Hypertonic saline (3% saline) infusion coupled with plasma copeptin measurement is an alternative test as the preferred test to be used in place of water deprivation test.

D : Hypertonic Saline Infusion Test

TESTING PROTOCOL

- Test overall lasts for about 3 hours.
- The patient lies in a supine position.
- Venous sampling is performed to obtain copeptin, serum sodium, glucose, urea, and plasma osmolality.

D : Hypertonic Saline Infusion Test

TESTING PROTOCOL

- Hypertonic saline infusion is commenced, initially with a bolus dose of 250 ml given over 10 – 15 minutes, followed by a slower infusion rate of 0.15 ml/Kg/min.
- Serum sodium and osmolality are measured every 30 minutes.
- The infusion is terminated once the serum sodium is ≥150 mOsm/L

D : Hypertonic Saline Infusion Test

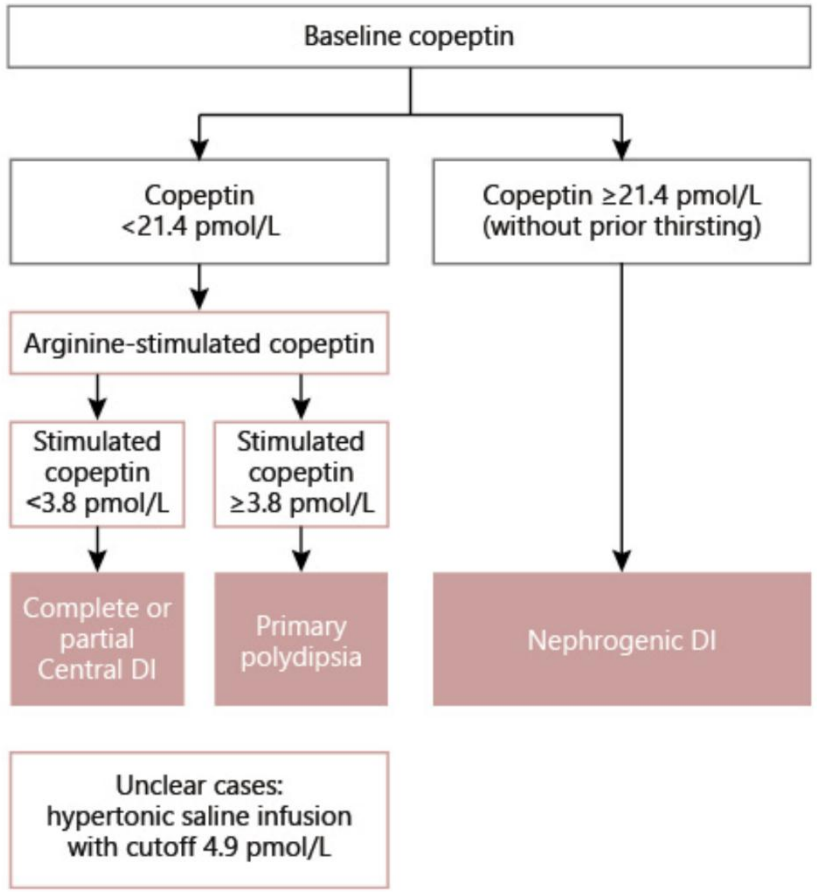
TESTING PROTOCOL

- Copeptin is measured and the patient is asked to drink water at 30ml/Kg within 30 minutes .
- This is followed by intravenous infusion of 5% glucose (dextrose) at 500 ml/hour for one hour .

TEST INTERPRETATION

- A plasma copeptin level of <4.9 pmol/L after hypertonic saline infusion indicates central DI (partial and complete) while a level of ≥4.9 pmol/L indicates primary polydipsia .
- It is likely that this cut-off value might be changed to 6.5 pmol/L .

E : Arginine Plus Copeptin



Nondiagnostic tests

- Therapeutic trial of desmopressin.
- For three days, desmopressin (10 mcg intranasally) is given in the evening and patients are advised to restrict their fluid intake to less than 1.5 to 2 L/day.
- Assessments of symptoms (thirst and polyuria), urine osmolality, and serum sodium are made twice daily.
- Careful monitoring during the trial of desmopressin is essential to promptly detect the development of hyponatremia.

3 - Identification of the underlying etiology

- In cases of central DI :

➢ Biochemical evaluation of pituitary hormones

➢ Brain MRI :

✓ macroadenomas, empty sella, infiltrative diseases

✓ absence of this bright spot

✓ Pituitary stalk thickness (> 2 mm)

➢ Genetic

Pituitary stalk thickness

- PST may be the first sign of a germinoma or Langerhans cell histiocytosis.
- Determination of tumor markers in blood and CSF helps in diagnosis.
- In idiopathic PST, repeat MRI and tumor marker estimation is done every 3 – 6 months during the first 3 years.
- Subsequently, MRI evaluation is performed once per year for 2 years and every 2 – 5 years thereafter, depending on the size and progression of the lesion.
- Biopsy is not recommended if PST is less than1.7 mm in diameter and is well delimited.

3 - Identification of the underlying etiology

- In cases of nephrogenic DI :

➢ Drugs (lithium, demeclocycline, cisplatin)

➢ Electrolyte abnormalities (hypercalcemia , hypokalemia)

➢ CRF (vascular, inflammatory, or neoplastic processes, polycystic kidney disease),

➢ Obstructive uropathy

➢ Systemic diseases (amyloidosis or sickle cell disease)

➢ Genetic

3 - Identification of the underlying etiology

- In cases of Primary polydipsia :

➢The dry mouth (anticholinergic)

➢Hypothalamic disease (sarcoidosis, tuberculosis, trauma, neoplasms)

Treatment of central diabetes insipidus

- The initial aim of therapy is to reduce nocturia.
- Once this is achieved, one aims for **partial** control of the diuresis during the day since complete control can lead to retention of water and hyponatremia.

Treatment of CDI

- ✓Providing free access to water
- ✓Dietary management to optimize free water excretion
- ✓Therapy with vasopressin analogue
- ✓Treatment of the underlying cause

Chlorpropamide, carbamazepine and clofibrate should **not** be used in children, since limited data suggest that they are less effective than desmopressin and have significant adverse effects

Treatment

- ***Free access to water***
- This facilitates maintenance of tonicity if the thirst mechanism is intact.
- Fluids alone can be a management strategy in very young infants and neonates.
- Long standing excess fluid intake may cause hydronephrosis and hydroureter and may also lead to fluorosis.

Treatment

- ***Dietary management***
- Diet with low sodium, low protein with high calories
- Restriction oral sodium intake to 1 meq/ kg/d and protein intake 2 g/kg/d.
- It is more prudent to restrict salt than proteins which are essential for growth.

Treatment of CDI

- ***Vasopressin and its analogue***
- **Desmopressin** is the current drug of choice for long-term therapy of CDI.
- It can be given parenterally, orally, or intranasally.

Treatment of CDI

- **Desmopressin**

❖Children older than 12 years of age :

The initial oral dose is 0.05 mg at bedtime

upper daily dose of 1.2 mg (divided two to three times a day)

The initial intranasal dose is 5 mcg at bedtime

upper daily dose of 40 mcg (divided two times a day)

Treatment of CDI

- **Desmopressin**

❖Children younger than 12 years of age :

The same initial desmopressin dose is used

but

upper daily limit of the oral medication is 0.8 mg

upper daily limit of the intranasal preparation is 30 mcg

Treatment of CDI

- First dose is typically given at bedtime.
- The size of and necessity for a daytime dose is determined by the effectiveness of the evening dose.
- If, for example, polyuria does not recur until noon, then one-half the evening dose may be sufficient at that time.

Treatment of CDI

- Desmopressin has also been developed as a sublingual (melt) formulation containing 60, 120, and 240 mcg.

Dose comparison of different formulation of desmopressin

Dose comparison	melt	tablets	spray
	60 µ	100 µ	2.5 µ
	120 µ	200 µ	5 µ
	240 µ	400 µ	10 µ

Treatment of CDI

❖**Infants and small children**

- Treatment challenging for the following reasons:

✓Oral or intranasal administration of desmopressin is difficult

✓Infants and small children are unable to both access fluids and articulate thirst to care providers.

✓It is often challenging to ascertain the volume of urine output in children who are not toilet trained.

✓Infants receive all or most of their nutrition in liquid form.

Treatment of CDI

- Two approaches are used to treat infants and small children:
  - low-solute diet plus thiazide diuretics
  - Intranasal or subcutaneous desmopressin

Treatment of CDI

➢ **low-solute diet plus thiazide diuretics**

- For infants who are dependent upon a milk diet, human milk is preferred because of lower solute load (75 mosmol/L) compared with :

➢ Similac (92)

➢ Regular cow milk-based formula (110)

➢ Soy-based formula (126)

➢ Cow's milk (235)

Example for renal solute load

- Suppose an infant with a daily intake of 750 mL of human milk has a maximum urine osmolality of 100 mosmol/kg.
- 1 L 75 mosmol ……. 0.75 L ? 56 mosmol (MILK)
- 100 mosmol 1L ……. 56 mosmol ? 0.56 L (URINE)

Example for renal solute load

- Changing to a regular cow milk-based formula :
- 1 L 110 mosmol ……. 0.75 L ? 83 mosmol
- 100 mosmol 1 L ……. 83 mosmol ? 0.83 L

Treatment of CDI

➢**low-solute diet plus thiazide diuretics**

- Oral hydrochlorothiazide is commonly used in infants up to six months of age at a dose of 2 to 3 mg/kg per day divided in two doses, maximum dose: 37.5 mg/day.
- The dose in older infants and small children is 2 mg/kg per day (divided in two doses).
- Hypovolemia-induced increase in proximal sodium and water reabsorption, thereby diminishing water delivery to the ADH-sensitive sites in the collecting tubules and reducing the urine output.

Treatment of CDI

➢ **Intranasal or subcutaneous desmopressin**

- Therapy with either a low intranasal dose of desmopressin or a small sublingual (melt) dose in symptomatic patients at around one year of age.

Monitoring

- The serum sodium should be measured one to two days after the initial dose of desmopressin as well as after any dose adjustment .
- If the serum sodium is normal at one to two days, repeat measurements at one and two weeks after dose initiation and then at every patient visit.
- In children on a stable dose of desmopressin, the serum sodium should be measured every one to two years.
- Infants should be weighed frequently.
- Urine osmolality 400 mosmol/kg

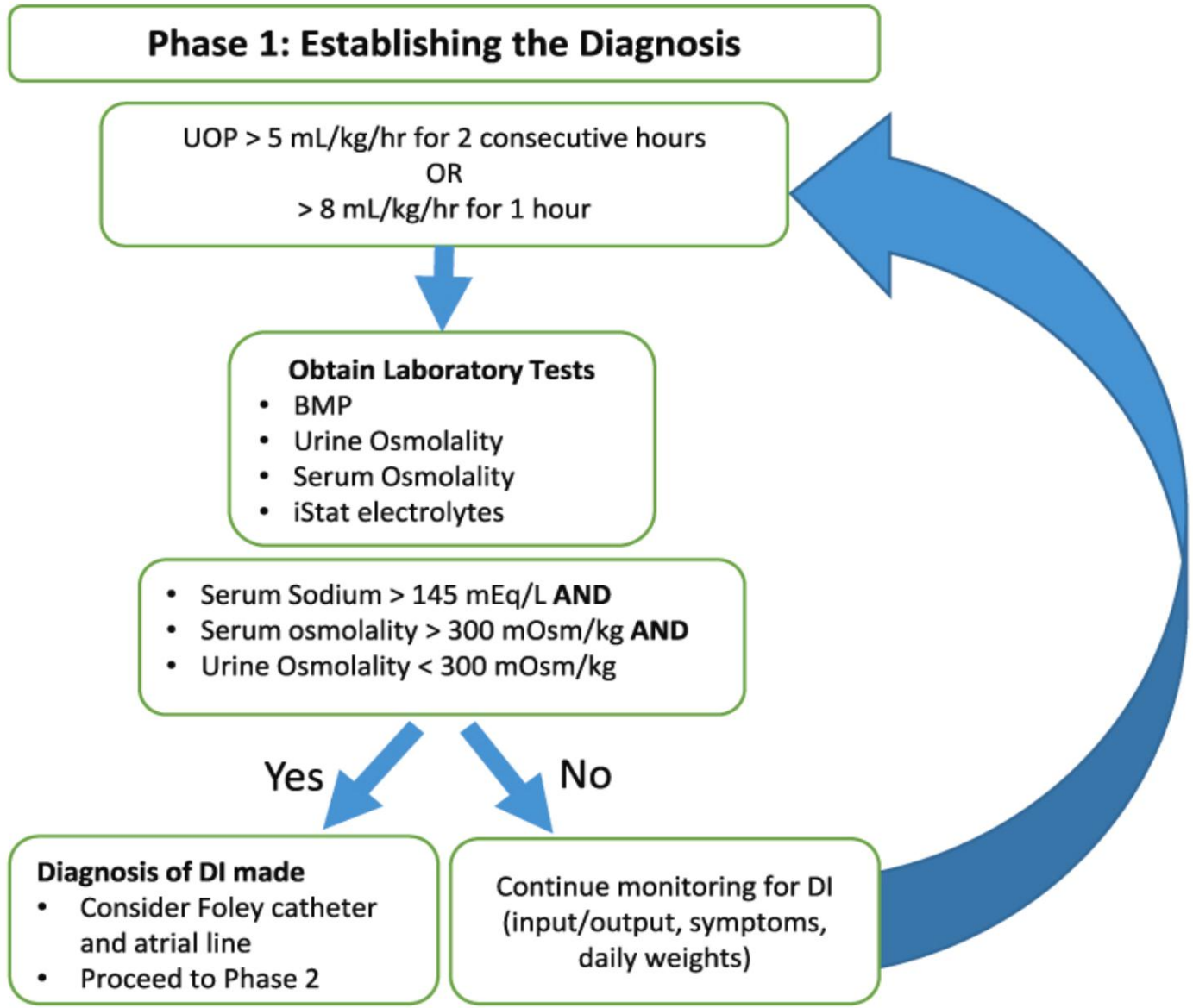
Treatment of Nephrogenic DI

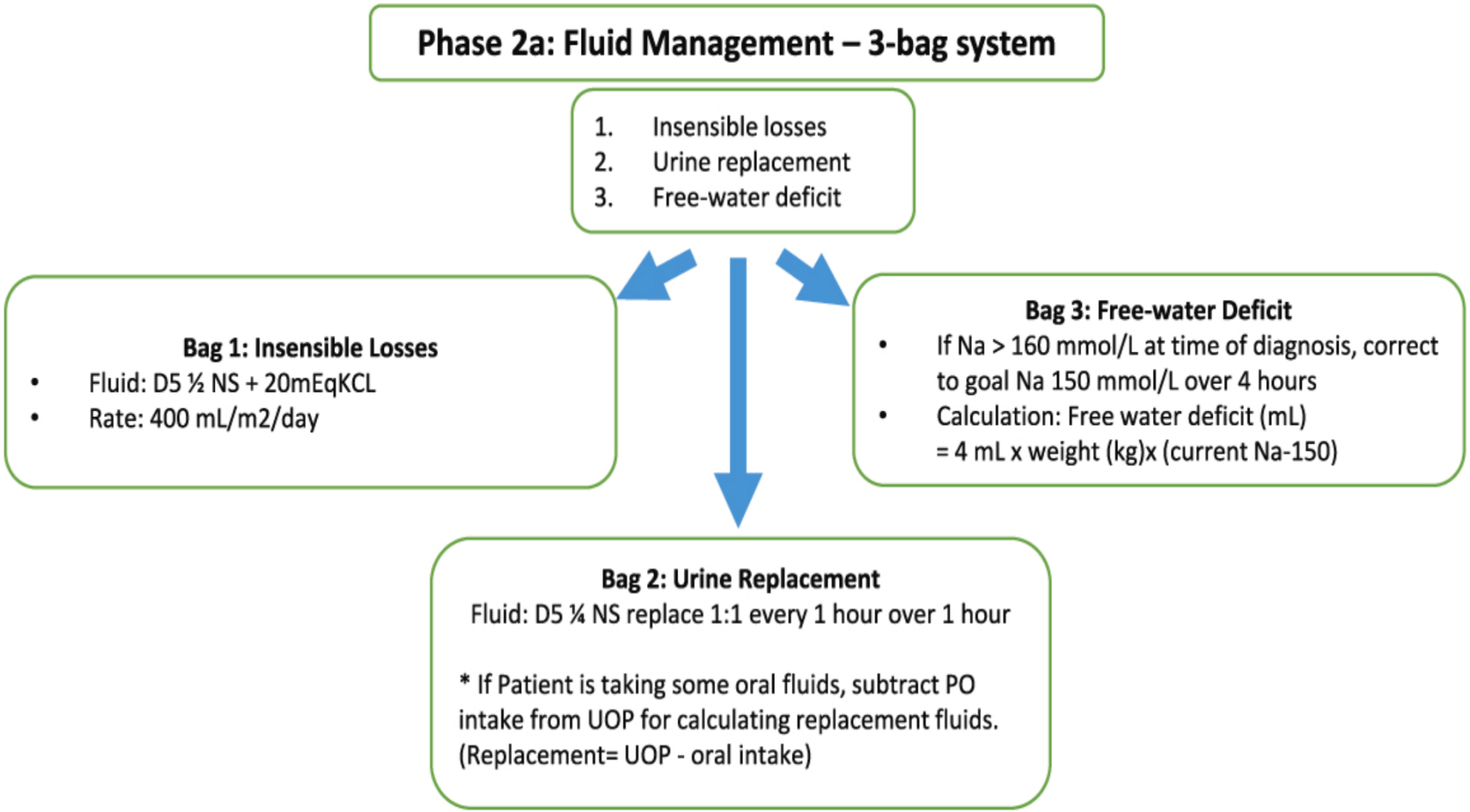
- Treatment of the underlying cause
- Providing access to free water
- Providing a high calorie to solute ratio
- Hydrochlorthiazide (2 - 4 mg/kg/day)
- Amelioride (0.3 mg/kg/d)
- Indomethacin (2 mg/kg/d)

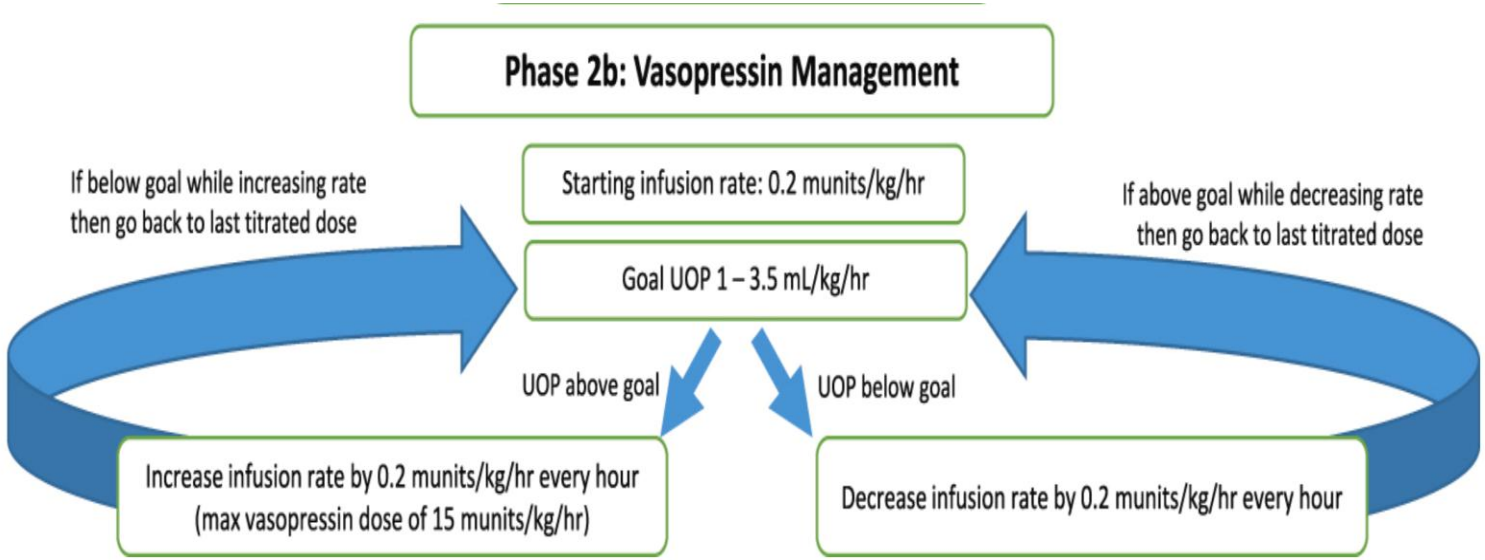
  Inhibiting the renal synthesis of prostaglandins, which are ADH antagonists
- High dose dDAVP

Standardized protocol for the management of diabetes insipidus in pediatric neurosurgical patients

Urine output	≥5 mL/kg/h for 2 consecutive hours **OR** >8 mL/kg/h for 1 h
Serum sodium	>145 mmol/L **OR** Increase by 8 mmol/L in 1 h
Osmolality	Serum >300 mOsmol/kg H_2O **AND** Urine <300 mOsmol/kg H_2O
Weight (with/without)	Loss >5% compared to a recent measurement


Phase 1: Establishing the Diagnosis
UOP > 5 mL/kg/hr for 2 consecutive hours
OR
> 8 mL/kg/hr for 1 hour
Obtain Laboratory Tests
• BMP
• Urine Osmolality
• Serum Osmolality
• iStat electrolytes
• Serum Sodium > 145 mEq/L AND
• Serum osmolality > 300 mOsm/kg AND
• Urine Osmolality < 300 mOsm/kg
Yes
No
Diagnosis of DI made
• Consider Foley catheter and atrial line
• Proceed to Phase 2
Continue monitoring for DI (input/output, symptoms, daily weights)


Phase 2a: Fluid Management – 3-bag system
1. Insensible losses
2. Urine replacement
3. Free-water deficit
Bag 1: Insensible Losses
• Fluid: D5 ½ NS + 20mEqKCL
• Rate: 400 mL/m2/day
Bag 3: Free-water Deficit
• If Na > 160 mmol/L at time of diagnosis, correct to goal Na 150 mmol/L over 4 hours
• Calculation: Free water deficit (mL) = 4 mL x weight (kg)x (current Na-150)
Bag 2: Urine Replacement
Fluid: D5 ¼ NS replace 1:1 every 1 hour over 1 hour
* If Patient is taking some oral fluids, subtract PO intake from UOP for calculating replacement fluids. (Replacement= UOP - oral intake)


Phase 2b: Vasopressin Management
Starting infusion rate: 0.2 munits/kg/hr
Goal UOP 1 – 3.5 mL/kg/hr
If below goal while increasing rate then go back to last titrated dose
If above goal while decreasing rate then go back to last titrated dose
UOP above goal
UOP below goal
Increase infusion rate by 0.2 munits/kg/hr every hour (max vasopressin dose of 15 munits/kg/hr)
Decrease infusion rate by 0.2 munits/kg/hr every hour

A known case of diabetes insipidus undergoing surgery

- If a known case of DI requires surgery and needs prolonged oral fluid restriction:

✓Usual dose of desmopressin is withheld prior to surgery.

✓Child is kept on 1 L/m^2/d of intravenous fluids.

✓When the effect of the previous desmopressin dose wanes off and CDI sets in, intravenous aqueous vasopressin is started as 0.5 mU/kg/hr.

A known case of Central DI receiving hydration therapy

- If a child with CDI is to receive high volume of fluid as part of hydration accompanying chemotherapy or forced dieresis, management of DI is difficult:

✓ Antidiuretic therapy needs to be discontinued

✓ Fluid intake should be increased to 3-5 $L/m^2/d$

✓ Low dose aqueous vasopressin (0.08 - 0.1 mU/kg/hr) infusion is recommended.

با تشکر