diabetes insipidus [created by Paul Young 30/11/07]

general

- diabetes insipidus is a syndrome characterised by polyuria, excessive thirst & polydipsia

central DI
- central or neurogenic DI results from an inappropriately low amount of ADH being released in response to an osmotic stimulus
- persistent severe central DI occurs rarely, as does DI which is precipitated by excessive intake of water caused by abnormalities of thirst or psychogenic function (dipsogenic or psychogenic DI)
- transient, usually incomplete, central DI is common severe head injury

nephrogenic DI
- caused by deficient action of ADH
- occurs very uncommonly in its classical form
- may be recognised as a less severe form acquired in patients on lithium therapy

physiology

(i) factors increasing ADH secretion:
- hyperosmolality
- hypotension
- stress, emotional stimuli
- pain, surgery, trauma
- exercise
- positive pressure ventilation
- cholinergic and beta adrenergic drugs
- nicotine, angiotensin II, barbiturates

(ii) ADH action is potentiated by:
- carbamazepine
- clofibrate
- thiazide diuretics
- prostaglandin synthetase inhibitors

(iii) ADH secretion is inhibited by:
- central DI
- opioid antagonists

(iv) ADH action is antagonised by:
- hypokalaemia
- hypercalcaemia
- prostaglandin E2
- lithium, amphotericin B
- excess vasopressinase

actions of ADH:
(i) antidiuresis
- results from ADH action on V2 receptors in the distal renal tubule, mainly in the collecting duct. V2 agonist action stimulates cAMP leading to activation of microtubule passages for water ingress

(ii) vasoconstriction
- vasoconstriction results from V1a receptor stimulation which occurs when higher concentrations of ADH exist. This is clinically significant in hypotensive states, where high concentrations of ADH contribute to the maintenance of blood pressure

(iii) coagulation
- coagulation effects are extrarenal V2 receptor mediated
- prostacyclin generation is stimulated; tPA, factor VIII coagulant activity and von Willebrand's factor all increase
- ADH & its analogues, in pharmacological doses, induce coagulant activity in healthy patients & in disease states and after cardiac surgery

normal relationship between plasma and urine osmolality

plasma osmolality	urine osmolality
>288	>125
>290	>200
>292	>400
>294	>600

differential diagnosis of polyuria

1. excess water load
(i) exogenous - iatrogenic, thirst disorders, hypothalamic disease, psychogenic polydipsia drugs (eg chlorpromazine, anticholinergics)
(ii) endogenous - recovery from unrecognised overload
2. solute (osmotic) diuresis
(i) exogenous or endogenous solute load - glucose, urea, mannitol, iv contrast, sodium choride
(ii) abnormal solute handling - chronic renal disease, diuretics
3. renal tubular unresponsiveness of ADH
(i) nephrogenic DI - congenital & familial
(ii) acquired nephrogenic DI - drug induced (lithium, clozapine, rifampicin, gentamycin), chronic electrolyte disturbance (hypercalcaemia), renal disease, post ATN, post renal transplant, amyloid, multiple myeloma, sickle cell disease, pregnancy
4. central DI
(i) neoplastic, infective or infiltrative lesions of the hypothalamus or pituitary
(ii) pituitary or hypothalamic surgery or ablative radiotherapy
(iii) head injury
(iv) vascular lesions (post partum necrosis, haemorrhage or hyperviscosity
(v) congenital (usually autosomal dominant)

central DI

aetiology:
- causes of persistent central DI invariably involves destruction of the hypothalamus or pituitary gland & sometimes produce defects in thirst mechanisms
- complete central DI may follow severe head injury & rarely even minor head trauma
- incomplete central DI occurs quite commonly with severe head injuries & particularly with brain death
- pituitary apoplexy continues to be described after hypovolaemia & septic shock
- transient DI has been described with thoracic trauma & CABG
- some causes (lithium & sarcoidosis) may have variable components of central & nephrogenic DI and thirst disorder

pathophysiology:
- the syndrome of DI results from a failure of appropriate ADH secretion or action, in response to the physiological stimulus of water deficiency which is characterised by relative plasma hyperosmolality
- if ADH deficiency is complete, over 20L/day of very dilute urine may be passed
- frequently ADH deficiency is relative with a reduction in the slope & sensitivity of the ADH response to a change in plasma tonicity, resulting in lesser amounts of hypotonic urine (3-6L/day)
- central DI is less severe in the presence of simultaneous failure of the anterior pituitary due to a lower cortisol level resulting in a lower metabolic rate, renal solute load, GFR & inhibition of free water excretion

presentation:
- usual clinical manifestations are sudden onset of polyuria with resultant thirst and polydipsia (in patients who are able to drink). In patients who are unable to drink hypernatraemia and volume depletion develop
- urine volumes >4-6L/day or 3ml/kg/hr for 4-6 consecutive hours in neurosurgical patients suggests DI
- in severe forms urine is very hypotonic (50-200mosm/kg) but in incomplete forms, particularly if hypovolaemia is present, urine osmolality may well rise well above plasma osmolality. [the essential feature is that urine osmolality is low compared to plasma osmolality]
- following neurosurgery on the hypothalamus and pituitary, four patterns of urine output have been observed:
(i) temporary polyuira lasting several days
(ii) transient polyuria followed by a period of normal urine output followed by permanent DI
(iii) an immediate and permanent polyuria
(iv) a variation of the triphasic pattern in which there is decreased urine output in the interphase

investigation:
- subjects with DI have higher plasma osmolalities but there is considerable overlap with the normal range and this determination is not diagnostic in individuals; urine osmolality is low (often 50-100mosm/kg) but the degree varies inversely with the severity of the polyuria
- solute diuresis (rather than DI) is suspected if the urine osmolality is between 250 & 320mosm/kg and particularly if there is an increased osmolar gap
- further testing include dehydration tests, DDAVP tests and ADH assays
- in practice DDAVP is administered 1-2mcg/kg sc 12hrly and response is observed

general management:
- management problems in the ICU are usually focussed on the polyuria & hypovolaemia with associated hyperosmolality
- rapid return to normal plasma osmolality is not always the major objective, particularly where an increase in cerebral volume is undesirable
- provided there is cardiovascular stability, mild polyuria (eg 3ml/kg/hr) is often best observed with frequent determinations of plasma and urine osmolality, unless hyperosmolaemia develops
- if polyuria is persistent or severe (eg>7ml/kg for >4-6hrs) drug therapy should be considered
- the priority is almost always restoration of circulatory stability rather than reversal of hyperosmolality
- if parasellar pathology is the suspected as the cause then anterior pituitary deficiency with steroid deficiency may coexist

specific therapy:
(i) vasopressin
- may be given by continuous infusion & is effective in reversing polyuria
- doses of 0.04U-0.1U per hour may be used
(ii) DDAVP (desmopressin)
- 1 to 2 mcg iv (larger doses are often required in early central DI) or 10-40mcg intranasally
- duration of action is 12-24hrs when given intranasally due to slow absorption
(iii) non-hormonal management
- these agents either increase renal sensitivity to ADH or potentiate ADH release & are only considered in partial central DI (eg thiazides, chlorpropamide, carbamazepine)

nephrogenic DI

congenital nephrogenic DI
- include congenital X-linked form (90%) & a less common autosomal form which may be either recessive or dominant
- hypercalcaemia, hypokalaemia & drugs that antagonise ADH will worsen the disorder & should be avoided

acquired nephrogenic DI
- occurs commonly in association with various drugs
- drug induced DI is always the nephrogenic type
- nephrogenic DI occurs in 10% of patients on long-term lithium even if it is in the therapeutic range

transient DI of pregnancy
- a vasopressin resistant DI of pregnancy is recognised
- this transient condition is caused by excessive placental generated vasopressinase
- there is a brisk response to DDAVP which is not metabolised by vasopressinase
- associated acute fatty liver and liver failure ahve been described