Clinical Endocrinology

Diabetes Insipidus

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In 1794 Frank¹ described diabetes insipidus as "a long continued abnormally increased secretion of non-saccharine urine not caused by renal disease," so distinguishing it from diabetes mellitus and the polyuria of chronic renal failure. In contrast, the definition of diabetes insipidus now usually given is of "a rare disease, characterized by polyuria and polydipsia, which results from lack of the antidiuretic hormone, arginine vasopressin".² The latter excludes not only habitual excessive (compulsive) water drinking,³ or potomania, but also functional renal defects, as occur with hypokalaemia or hypercalcaemia, or even the inherited defect that prevents vasopressin acting effectively on the renal tubules (the so-called nephrogenic diabetes insipidus).

This definition is the most useful for recognizing those in need of vasopressin treatment (or trial of one of the oral agents that can sometimes replace it). But this article will also consider the whole clinical problem of excessive thirst and polyuria, not least because of the circular relationship between the two prime symptoms and states of hydration (see Figure, outer circle) and because of the inter-locking relationship in which over-hydration both lowers the circulating vasopressin and reduces its renal activity, so mimicking "deficiency" and "nephrogenic" diabetes insipidus, respectively (Figure, inner left). Hence, diagnosis of habitual water drinking from diabetes insipidus may be impossible without an initial period of fluid restriction.

Differential Diagnosis of Thirst and Polyuria

These complaints are easily understood, but not always emphasized by patients, and inquiry about excessive thirst is easily omitted from routine questioning. As with any symptom, it is important to get some idea of its degree. Patients complaining strongly of "thirst" because of salivary gland disease may drink less than 3 l. daily. Urinary frequency alone is usually easily distinguished from polyuria because of the lack of polydipsia and the realization by the patients that they pass only small volumes of urine at a time.

Once the symptoms are established simple ward or laboratory tests on urine or blood probably carry one furthest in narrowing the diagnostic field. Nevertheless, as always, history and examination may give important leads—for example, the weight loss of diabetes mellitus; a history of "stones and groans" in hyperparathyroidism; muscle weakness in hypokalaemia; or the unusual "life situation" common in habitual water drinking. Pathognomonic features are few, however, but include visual field defects from a craniopharyngioma or the strong family history (among males) of hereditary nephrogenic diabetes insipidus.

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When the results of screening tests (Table I) show no explanation for polyuria and polydipsia, further investigation of the patient is needed. This will often require hospital admission, for even if the x-ray film of the pituitary fossa is abnormal the nature of the lesion will have to be determined, the pituitary function assessed, and the patient's response to treatment determined.

TABLE I—Screening Tests for "Polyuria and Polydipsia"

Urine:		
Microscopy		Cells, casts, organisms suggesting chronic renal disease
Specific Gravity		1.005 or less in diabetes insipidus and usually equally low in habitual water drinking. Fixed around 1.010 in severe renal impairment but may be much lower. High in diabetes mellitus
Glucose		Clinistix or Clinitest
Calcium		Sulkowitch's ammonium oxalate reagent
Osmolality		For comparison with serum
Blood:		
Blood urea, glucose and (plasma) calcium and potassium		
Packed cell volume (and haemoglobin)		
Osmolality. Even casual values are of "weighting" value, tending to be high in diabetes insipidus and low in habitual water drinking—but the ranges for casual values overlap considerably		
Radiology:		
Pituitary fossa and chest		

Clinical Features

Vasopressin deficiency is divided into primary and secondary groups.⁴ The primary group has two divisions. The first type is idiopathic deficiency, which is a common cause of this rare disease. It affects the sexes equally and may begin at any age after infancy, and histologically is associated with a striking reduction in the number of neurones in the supraoptic and paraventricular hypothalamic nuclei.⁵ The second type is a very rare familial type affecting both sexes, often having an onset in infancy and again being associated with a great reduction of neurones in the two nuclei.⁵

By contrast, the secondary group includes lesions of the posterior pituitary or of the pituitary stalk. Tumours of the pituitary itself (most often chromophobe adenomas) or craniopharyngiomas still comprise most of this group. Rupture of the pituitary stalk secondary to trauma as from a car accident is now becoming increasingly frequent; in this case anosmia (at least on one side) may also be present. Iatrogenic diabetes insipidus is another cause being increasingly seen, now that operation on primary pituitary tumours is undertaken more readily and hypophysectomy is used to treat disseminated carcinoma. Other causes of the secondary group are listed in Table II.

TABLE II—Classification of "True" Diabetes Insipidus

Primary	(1) Idiopathic
	(2) Familial
Secondary	(1) Pituitary tumours (primary and secondary)
	(2) Craniopharyngioma; other tumours adjacent to pituitary or hypothalamus
	(3) Iatrogenic (postoperative)
	(4) Traumatic, including birth injury
	(5) Granulomata (sarcoidosis, eosinophilic granuloma, brucellosis, tuberculosis, syphilis)
	(6) Rarely associated with Sheehan's syndrome; and sickle-cell disease

concentration. Nevertheless, nicotine is often a more potent stimulus to vasopressin release than plasma hypertonicity,²¹ though unfortunately nicotine for intravenous injection is now extremely difficult to obtain in this country.

ROUTINE OF STUDIES

A recommended routine for investigation of suspected diabetes insipidus is given below (see Table I).

- (1) Tests as in Table I. Random urine and plasma osmolality.
- (2) 24-hour fluid intake and output during unrestricted access to fluid. Measure early morning plasma and urine osmolality.
- (3) Fluid deprivation test for six hours,¹⁷ after sleep and four hours standardized fluid intake.
- (4) If doubt of diagnosis remains use:
 - (a) Procedure of Miller *et al.*¹⁹ and
 - (b) Procedure of Barlow and de Wardener³ or both, and
 - (c) Retest after achieving diminished fluid turnover for two weeks
- (5) If failure of vasopressin activity diagnosed by (3) or (4) test response to vasopressin, 5 IU SC to distinguish nephrogenic from intracranial causes.

Before launching more complex tests it is always worthwhile to obtain random urine and plasma samples for osmolality, since fundamentally diabetes insipidus is a dehydrating condition and compulsive water drinking one that dilutes body fluids.³ The 24-hour fluid balance during unrestricted access to fluid should also be recorded, with measurement of the overnight osmolalities—for surprising results may be found which make the physical problem appear much less than one had supposed.

Finally, it must be realized that initial tests may not give conclusive answers—either because of a partial defect in vasopressin production or a temporary result of over-hydration.²² Hence by a regimen of partial fluid restriction (for example, to 2 l./day), or with the help of a course of vasopressin, the doctor should try to achieve something akin to a normal fluid balance in the patient for at least two weeks before retesting.

Treatment

The conventional treatment of diabetes insipidus is by replacement of vasopressin. Unfortunately, this cannot be taken by mouth, but is available for intramuscular or intravenous injection, or it can be absorbed through the nasal mucosa. Perhaps because of this inconvenience of administration, a variety of oral agents have now been found to ameliorate diabetes insipidus, by mechanisms not wholly understood.

Aqueous vasopressin has too short an action to be acceptable for long-sustained treatment. It is used in diagnosis and is of great value in treating a rapidly changing clinical picture when the patient is in hospital—for example, after a head injury or an operation on a pituitary tumour—since in these situations phases of diuresis and antidiuresis may rapidly succeed one another. A typical intramuscular dose is from 0.5 to 0.1 IU, which acts for 1 to 2 hours. It may also be usefully added to an intravenous infusion.

Vasopressin tannate in oil is given intramuscularly—in principle as required, though often an injection once every 24 to 48 hours copes well. If the next injection is taken before polyuria has returned there is a risk of water intoxication. To achieve a reliable dosage the suspension must be warmed to blood heat and shaken thoroughly before injection. The injection site should be varied regularly, or else a large subcutaneous depot accumulates, mostly of oil, which acts as a buffer to reliable absorption. Vasopressin tannate is a satisfactory agent, to which resistance rarely develops, in contrast to the nasal preparations, whose efficacy (however convenient) often survives for only five to ten years at the most.

The resistance partly depends on the development of atrophic rhinitis secondary to the vasoconstrictive action of the drug, but use of posterior pituitary powder as snuff may also lead to attacks of brochospsasm through sensitization.

LYSINE VASOPRESSIN

Lysine vasopressin is available as a spray (5 ml to the bottle, 50 IU/ml) taken as one or two sniffs up each nostril; these often need to be repeated every two to four hours. Its action may be prolonged by inserting a pledget of cotton wool soaked in the solution into a nostril, but even then it rarely lasts a night through. Lysine vasopressin is also absorbed through buccal or vaginal mucosa. Though relatively costly and resistance often develops within a few years, it is clearly a real convenience and may be very useful as a standby at special times, as on a journey.

The oral agents²³ for treating diabetes insipidus are now a motley bunch. The thiazides, in conventional doses, reduce polyuria in both “deficiency” diabetes insipidus and the inherited nephrogenic form. No one has yet explained exactly how they act but their effects may resemble those produced by dietary sodium deprivation or failure of the anterior pituitary (when there is decrease in appetite and a reduction in the filtered solute load.) Not unexpectedly, therefore, the related furosemide and the unrelated ethacrynic acid have both relieved diabetes insipidus.

SULPHONYLUREAS

Though it has some chemical similarity, chlorpropamide²⁴ acts differently from the thiazides, and is of no help in nephrogenic diabetes insipidus. Given intravenously, chlorpropamide acts rapidly, but the usual oral dose takes 24 hours to begin to work, and 72–96 hours to be fully effective; its action wears off equally slowly. Its activity in diabetes insipidus is not shown equally by other sulphonylurea hypoglycaemic agents tested. It augments the effect of inadequate amounts of vasopressin,²⁵ and may therefore be ineffective when vasopressin is completely absent. Water restriction increases the effectiveness of chlorpropamide, while ethanol nullifies it. Not surprisingly, therefore, hyponatraemia can occur during chlorpropamide treatment if it “over-amplifies” the effect of the amount of vasopressin present (which in partial lesions of the posterior pituitary might vary considerably). Such hyponatraemia—or indeed any manifestation of water intoxication during treatment—can occur only if the patient drinks fluid by custom rather than in response to thirst. Indeed, the patient with diabetes insipidus can never come to harm, treated or untreated, if he follows the maxim “drink whenever, but only whenever, you are thirsty”, unless the mechanisms subserving thirst are working normally. Sometimes, indeed, these mechanisms are disrupted by the lesions responsible for the diabetes insipidus, and then drinking must again become a matter of habit.

It seems reasonable to expect that if intramuscular vasopressin and chlorpropamide were combined the frequency of injections (or their size) could be reduced, but there is little experience of how smoothly this combination would act or how severely fluid intake would have to be restricted on the day of the vasopressin injection.

OTHER AGENTS

Two other agents have, perhaps unexpectedly, also proved effective against diabetes insipidus. These are, firstly, Tegretol²⁶ (carbamoyl-dibenzo-azepine), 200 mg two to four times daily, taking 24–48 hours to begin to act, potentiated by chlorpropamide, working despite ethanol ingestion, and ineffective with nephrogenic patients. Secondly, clofibrate,²⁷ 500 mg four times

daily, again takes two to three days to work and is also useful only when some vasopressin is present.

On present limited experience the best of the oral agents would seem to be chlorpropamide, which is effective in reducing symptoms to an acceptable level in one-third to one-half of patients. Its use is associated with a small incidence of sensitivity reactions and gastrointestinal symptoms; a low but definite incidence of serious blood dyscrasia (it should never be used in a dose above 500 mg a day); a liability to attacks of flushing and fainting after alcohol; and occasional occurrence of hypoglycaemia—perhaps particularly to be expected in those tending to “reactive hypoglycaemia,” especially if this is an early manifestation of “maturity-type onset” diabetes mellitus.

Prognosis

This is excellent for life, unless affected by a “secondary” cause of the diabetes insipidus. The condition is perhaps less often permanent than is usual with endocrine deficiency states, and trial of cessation of therapy after, say, two and again five years should be attempted in this condition—which is essentially a “nuisance” one—provided proper watch is then kept for the effects of an acquired “polydipsic drive.”

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One Hundred Years Ago

From the *British Medical Journal*, 13 April 1872

WHY ARE CASES OF JOINT-DISEASE INVARIABLY WORSE DURING THE WARM MOIST DAYS OF WINTER?

Sir,—This question, recently propounded by the Editor of the *British Medical Journal*, at the termination of some remarks on Mr. Wood's experience at King's College Hospital with reference to joint-affections, may have some light thrown on it by the following considerations. The rustic is informed by his sensations, and the dweller in towns by his barometer and hygrometer, concerning the coming weather. The former is of opinion that toothache, cornache, and pains of the joints; and the latter, that a decrease in the pressure, an excess of humidity, and an increase of the temperature of the air, are precursors of foul weather. Meteorologists all know that the warm and moist equatorial current is generally accompanied in winter by a decrease of barometric pressure. How clearly did the great Jenner embody in a few lines of verse. “On the Signs of Rain,” the effects of these atmospheric changes:

“Hark! how the chairs and tables crack,
Old Betty's joints are on the rack.”

The aching of corns is as readily accounted for as the cracking of chairs and tables; for both are evidently the result of the increase of the amount of moisture in the air. The great alterations in size which epithelial and ligneous structures undergo by the addition or subtraction of moisture are well known; what are the changes in the body when it is exposed to low barometric pressure?

Richardson, Hewson, and others tell us that there is a tendency to exudation of fluid from wounded surfaces, a feebleness in the healing of wounds, a susceptibility to disturbance in the body generally, and a proneness to the production of secondary fever by the absorption of discharges which have undergone some decomposition. The outcome of these facts has been the establishment of the law, that no important surgical operation should be performed when the barometer is low, or when it is steadily falling. The principal effect, however, of diminished pressure of the atmosphere is distension of the capillaries. We all recognise as one of the exciting causes of apoplectic seizures a rapid diminution of atmospheric pressure, producing a sudden capillary engorgement. An exacerbation of the symptoms in cases of joint-disease may be due, perhaps to the same meteorological change acting in a manner which may be thus explained. In the solid inelastic articular expansions of the bones, which are surrounded by firm inextensible textures forming the joints, the minute nerves, shown by Kölliker and others to permeate the cancellous and compact structures in company with vessels, are pressed by these vessels when enlarged against the unyielding walls of the channels through which they pass. Although the nerves of bones do not generally afford healthy individuals any conscious sensations; yet, in diseases of the joints, the bones, when congested, or the seat of inflammation, become painful. . . .

I am, etc., CORNELIUS B. FOX, M.D., F.M.S.
Scarborough, March 1872.