Hereditary central diabetes insipidus: plasma levels of antidiuretic hormone in a family with a possible osmoreceptor defect

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A large Canadian kindred of Irish extraction extending from Quebec to British Columbia with autosomal dominant diabetes insipidus responsive to exogenous antidiuretic hormone (ADH) is described. Out of 121 individuals 34 have been identified as affected in seven generations. The disorder is characterized by variability in age at onset and in severity, and by apparently spontaneous abatement in old age. The affected subjects do not appear to manifest hypertension or its sequelae. In three individuals tested the plasma ADH level was very low in spite of adequate osmotic stimulation. However, the level rose in two of them when they were given furosemide, which suggests an osmoreceptor defect and a normal ADH response to volume change.

Description d'une vaste famille d'origine irlandaise répandue du Québec à la Colombie-britannique et présentant un diabète insipide dominant autosomique pitressinosensible. De 121 individus répartis sur sept générations, 34 sont atteints. La maladie se caractérise par la variabilité de l'âge du début et de la gravité, et par l'amendement apparemment spontané dans la vieillesse. On n'observe ni l'hypertension artérielle ni ses séquelles. Chez trois sujets étudiés, la concentration plasmatique de l'hormone anti-diurétique (HAD) reste très faible même en présence d'un stimulus osmotique suffisant. Mais elle s'élève chez deux d'entre eux après l'administration de furosémide, ce qui fait croire à une anomalie des osmorécepteurs et à la conservation d'une sécrétion normale d'HAD sous stimulus volumique.

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Diabetes insipidus is characterized by polyuria and polydipsia due to an abnormality in the regulation of water metabolism. The abnormality may be central (pituitary or hypothalamic) or renal in origin. In the first instance, central or neurohypophyseal diabetes insipidus, there is either a deficiency of antidiuretic hormone (ADH), which may be absolute or partial, or defective functioning of the osmoreceptor controlling the release of ADH — so-called resetting of the osmostat.[1,2] Renal or nephrogenic diabetes insipidus is due to unresponsiveness of the renal tubule to ADH. Either type of diabetes insipidus may be primary or secondary. The primary central form is most often idiopathic,[3] but a number of hereditary cases, usually with dominant inheritance, have been described. On the other hand, primary nephrogenic diabetes insipidus is always hereditary and probably always X-linked.[4]

Until 1970 the diagnosis of diabetes insipidus rested on demonstrating inability to concentrate the urine after an appropriate period of dehydration.[5] In 1970 Robertson and colleagues[6] developed a radioimmunoassay for plasma ADH, and since then a number of other laboratories have developed similar assays. These are not easy to perform, however, being subject to a number of special technical problems[7] and limited by the extremely low physiologic concentrations of ADH (about 10^{-12} *M*) in the blood. Therefore, measurement of the plasma ADH level has not become widely available; however, when reliably performed it can be an important aid in the diagnosis of diabetes insipidus, provided that its result is interpreted in relation to the serum or urine osmolality, or both. In this way the plasma levels of ADH have been found to be low in central and high in nephrogenic diabetes insipidus.[8]

We report here a large Canadian kindred with autosomal dominant central diabetes insipidus, in some of whom measurements of the plasma ADH level have been performed. To our knowledge there are only two other reports of such measurements in this rare disease.[9,10] In an attempt to further elucidate the pathogenesis of this disorder, we studied the response of the plasma ADH level to volume depletion with furosemide in two of the affected members.

Methods

In the subjects in whom diabetes insipidus was suspected, dehydration tests were performed following the protocol of Miller and associates.[5] The individuals were deprived of fluid overnight, then in the morning the urine osmolality was measured hourly, by freezing-point depression, until it plateaued, varying less than 30 mmol/kg over 3 hours. At that point 5 U of aqueous ADH (Pitressin) was injected subcutaneously, and an hour later the urine osmolality was measured once again. The difference between the osmolalities before and after the ADH injection was then calculated, and central diabetes insipidus was diagnosed if there was an increment of more than 9% after the injection.

In assessing one patient's response to sulfonylureas, 1 g of tolbutamide was injected intravenously, and the response was monitored by measuring the urine volume, the urine osmolality and the free water clearance.

Plasma ADH levels were measured by radioimmunoassay by the method of Hammer.[11] Blood was collected in tubes containing EDTA (edetic acid) and placed immediately on ice. The plasma was then separated and stored at −20°C till the assay was performed. Samples were collected following at least 45

minutes of recumbency from 13 nonsmoking volunteers without diabetes insipidus from outside the family, who had fasted and been deprived of fluid overnight, for the construction of an ADH/serum osmolality nomogram, as recommended by Zerbe and Robertson.[8] Samples were then obtained from the patients in the same conditions when they had stopped taking medication (desmopressin acetate or chlorpropamide) for 48 hours.

After this phase of the study five volunteers, three clinically affected family members and one unaffected family member continued the fasting and fluid deprivation and were given furosemide orally (children receiving 20 mg and adults 60 mg, except in the case of one elderly subject, who was given 40 mg). This added an acute volume depletion to the overnight dehydration. The individuals were then ambulatory for 4 hours or until thirst became excessive. At the end of that period blood samples were taken once again for measurement of the serum osmolality and the plasma ADH level.

All the subjects had given informed consent.

Family description and representative case histories

The pedigree (Fig. 1) was ascertained by personal interviews with three affected family members; they and their children were the subjects of our testing. Another 10 representative family members were contacted by phone. Individuals were categorized as affected only if they were said to be by 2 of the 13 members interviewed. We strongly suspect, but have been unable to prove, that this is only one kindred, as both progenitors (I-1 and II-1) came from Ulster, Ireland and had the same surname. The kindred is now distributed from Quebec to British Columbia, though some members live in the United States. We have not been able to demonstrate a relationship between these individuals and three other Canadian families with autosomal dominant central diabetes insipidus.[12-14]

As Fig. 1 shows, 34 individuals out of the 121 in seven generations were affected, in a pattern consistent with autosomal dominant inheritance. The male:female ratio was 19:15 (not significantly different, by chi-square analysis, from 1:1). The treatment of 19 individuals was unknown but was most likely negligible, as they were elderly. Seven had declined therapy, five were taking chlorpropamide (by self-prescription at the suggestion of relatives in two instances), and three were taking desmopressin acetate. Some of those who declined treatment had not been formally tested and were adapted to a fluid intake/output of 8 L/24 h or greater.

The proband (V-28) was referred to one of us (P.M.C.) at age 61 with a lifelong history of polyuria and polydipsia. Physical examination and routine investigations, including skull roentgenography and renal function studies, yielded nothing abnormal. The urine volume ranged from 5250 to 6150 mL/24 h. After overnight fluid deprivation the urine and serum osmolalities were 392 and 322 mmol/kg respectively (the maximum values after dehydration in persons without diabetes insipidus are more than 1000 mmol/kg[5] and 280 to 300 mmol/kg respectively). After the ADH injection the urine osmolality rose 21%, to 475 mmol/kg, and the serum osmolality fell to 315 mmol/kg. During treatment with chlorpropamide, 500 mg daily, the urine volume fell to an average of 2.5 L/24 h.

Patient VI-34, a daughter of the proband, was first investigated when she was 23 years of age. The history of her condition was identical, with a fluid intake/output ranging from 8 to 9 L/24 h without treatment. Administration of ADH after overnight dehydration caused the urine osmolality to rise 34% (from 448 to 600 mmol/kg). Table I shows the patient's response to tolbutamide; this sulfonylurea, similar to chlorpropamide, reduced the urine flow and the free water clearance, as well as increasing the urine osmolality. The patient also noted a worsening of

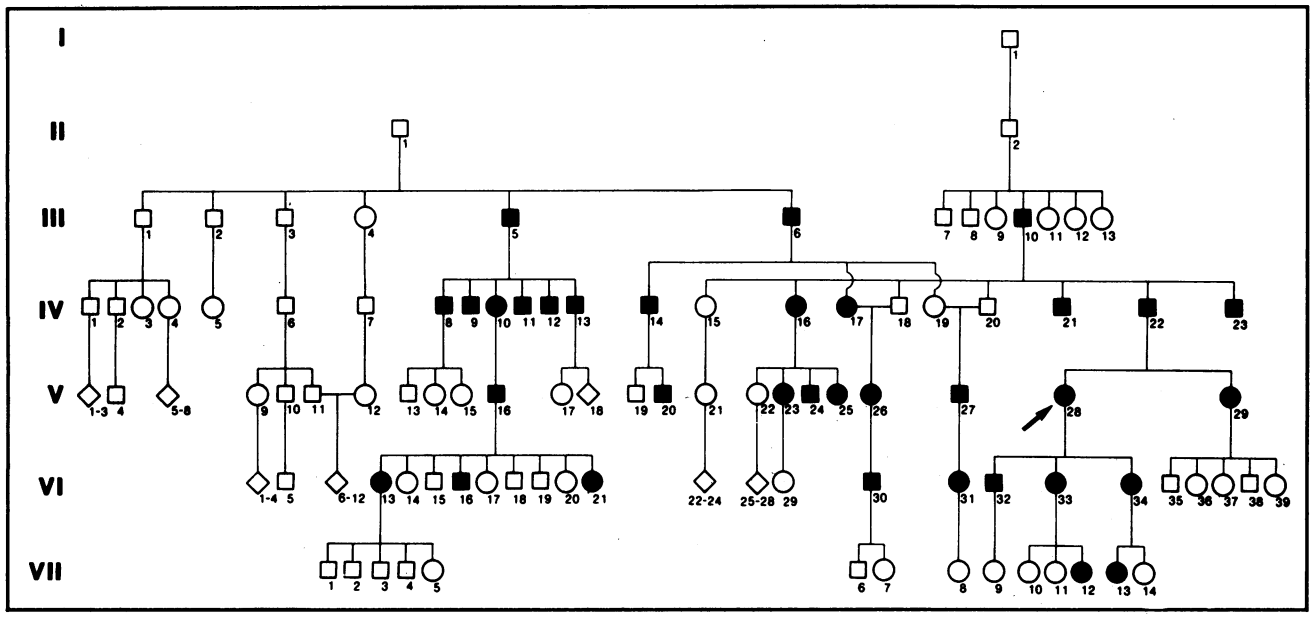

Fig. 1—Pedigree of kindred with central diabetes insipidus, showing autosomal dominant inheritance. Black symbols represent affected individuals; arrow indicates proband. Squares represent males, circles females and diamonds persons of unknown sex.

her diabetes insipidus during pregnancy and an amelioration during labour.

Other defining characteristics of the disorder in this family were the following: gradual onset of symptoms, most often dating from infancy, but in some cases from up to adolescence; absence of early death attributable to the disease; and variable severity, with a peak in early adulthood and abatement in old age. All 13 of the subjects with diabetes insipidus who were interviewed reported good general health and no hypertensive or cardiovascular disease in themselves or their affected relatives. Survival into the ninth decade was common and was ascertained in 10 out of 14 individuals in generations III and IV.

Results of ADH assays

Plasma ADH values were obtained for four clinically affected family members (V-28, VI-32, VI-34 and VII-13) and two unaffected members (VII-9 and VII-14). The diagnosis was confirmed in the three affected adults (V-28, VI-32 and VI-34): their ADH values were 0.7, 2.5 and 3.3 μg/L, with simultaneous serum osmolalities of 311, 310 and 318 mmol/kg respectively. These results are shown in Fig. 2 along with those for the unaffected volunteers.

Patient VII-13, aged 7 years, had mild clinical features of the disease, with an average fluid intake/output of 3.5 L/24 h and habitual urination twice a night. She was not receiving treatment. It is uncertain whether her overnight dehydration was effective; thus, although her plasma ADH level in relation to the serum osmolality (3.6 μg/L and 286 mmol/kg respectively) fell within the normal limits established from the volunteers, we regarded the result as nondiagnostic.

Fig. 3 shows that the plasma ADH levels increased after administration of furosemide in all four family members (one unaffected) and all five volunteers tested. The results did not help to further separate those affected from those unaffected.

Discussion

Hereditary diabetes insipidus was first described by Lacombe,[15] in 1841. Two large pedigrees in Germany with dominant inheritance were described in the late 1800s and early 1900s;[16-19] the responsiveness of some of these patients to posterior pituitary powder, first available in 1913,[20] suggests that they had central diabetes insipidus. Three Canadian families with dominantly inherited central diabetes insipidus have previously been described,[12-14] and there are a small number of other reports in which both a dominant mode of inheritance and central origin are well documented.[21-24] On the other hand, Forssman[25] reported on two ADH-responsive families with X-linked recessive inheritance, which implies that there are at least two types of central diabetes insipidus.

The family that we have described has central diabetes insipidus, as evidenced by the responsiveness of the disorder to exogenous ADH. The mode of inheritance conforms to an autosomal dominant pattern. The several instances of father-to-son transmission are inconsistent with X-linked inheritance. Although we did not test any of these father/son pairs, we believe that the family could reliably distinguish between affected and unaffected members. The male:female ratio of the affected individuals is not significantly different from 1:1 and thus does not support the suggestion by others[22,25] that a male preponderance exists. The older literature may have included, and confused, X-linked pedigrees with autosomal dominant ones.

Our patients' therapeutic response to chlorpropamide agrees with experience previously reported.[14] Their response to an intravenous injection of tolbutamide contrasts with Moses and coworkers' finding that tolbutamide was ineffective in the long-term oral treatment of patients with diabetes insipidus.[3]

The variability in age at onset and in severity, with worsening during pregnancy and abatement with ageing, has previously been described in hereditary central diabetes insipidus.[21-24] On the other hand, the absence of hypertension or of hypertension-related deaths has not been remarked upon. It may be coincidental but is of interest that Johnson and Buggy[26] demonstrated that the anteroventral third ventricular region in the hypothalamus influences both blood pressure regulation and

Table I—Response of patient VI-34 to intravenous injection of 1 g of tolbutamide

Measure	Before injection	After injection
Urine volume (mL/min)	0.87	0.50
Urine osmolality (mmol/kg)	419	690
Free water clearance (mL/min)	0.32	−0.62

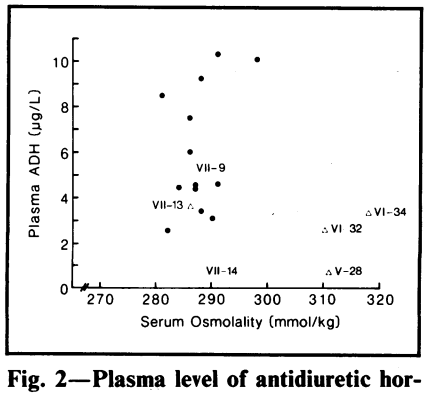

Fig. 2—Plasma level of antidiuretic hormone (ADH) in relation to plasma osmolality in clinically affected family members (white triangles), unaffected family members (white circles) and volunteers without diabetes insipidus from outside the family (black circles).

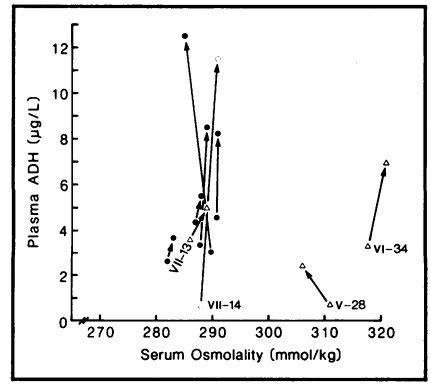

Fig. 3—Plasma ADH levels after overnight dehydration and then after administration of furosemide in clinically affected family members, one unaffected family member and volunteers without diabetes insipidus (symbols as in Fig. 2).

ADH release in the rat. A defect in the hypothalamus in our patients could have caused both the deficiency of ADH and the absence of hypertension. An alternative explanation may be that ADH is, per se, a hypertensive hormone in physiologic conditions. This controversial point is the cause of considerable recent research.[27]

The basic defect in hereditary central diabetes insipidus is not known. Two autopsy reports, those of Green and Braverman and their colleagues,[28,29] concern middle-aged adults and are strikingly similar in showing a loss of nerve cells in the supraoptic and paraventricular nuclei of the hypothalamus. These findings are also similar to those in reported cases of idiopathic central diabetes insipidus.[3,30] Hanhart[31] and Gaupp[32] also found at autopsy a 70% reduction in the corresponding nuclei, in one hereditary case each. It has been suggested that the inherited trait may be a tendency for involution of a specific region of the hypothalamus,[9] and it may be for this reason that the disorder is not manifest at birth but develops gradually thereafter. Serial measurements of the plasma ADH level in affected individuals should be helpful in testing this hypothesis. We plan to do this in patient VII-13.

If, on the other hand, the defect were in the synthesis of ADH, as in the Brattleboro rat,[33] one would expect heterozygous individuals to have approximately half the normal levels of ADH. This was not the case in two previous reports[9,10] or in our patients. Bruguier and associates[10] measured ADH levels in an affected child, and, while no details were given regarding the assay used or the concomitant serum and urine osmolalities, the ADH levels were consistently less than 1 μg/L. Kaplowitz and coworkers' two patients had ADH levels at the limit of sensitivity of the assay (0.5 μg/L) in spite of an appropriate osmotic stimulus (dehydration or infusion of hypertonic saline), although blood levels in the patient with a clinically milder form of the disease reached a detectable value (4 μg/L) transiently.[9] Our three adult patients were also clearly osmotically stimulated (with serum osmolalities of at least 310 mmol/kg), and the highest ADH value obtained was 3.3 μg/L, although all three had detectable levels. The assay that we used had a sensitivity limit identical to that of Kaplowitz and coworkers' assay but an upper limit of normal of 13 μg/L rather than 10 μg/L. Thus, under osmotic stimulation at least, our patients are more severely impaired than one would expect if their defect were simply in the production of ADH.

We therefore tested the hypothesis that ADH was present but unresponsive to osmotic stimulation in these patients by submitting two of them to mild volume depletion with the diuretic furosemide. It is known that osmolality plays an important part in the day-to-day regulation of ADH secretion but that decreases in volume (e.g., due to hemorrhage) are the most potent stimuli to ADH release.[1] The fact that our patients' ADH values increased to 2.4 and 7.0 μg/L from 0.7 and 3.3 μg/L could indicate a normal response to normally functioning volume receptors, which are located mainly in the right and left atria, the aortic arch and the carotid arteries. The defect in these subjects, therefore, may reside in the hypothalamic osmoreceptor, and this would account for the low ADH values after osmotic stimulation alone. Selective involvement of hypothalamic osmoreceptors has also been proposed in a patient with histiocytosis who was able to concentrate her urine in response to tilting, which stimulates volume receptors, but not in response to a variety of osmotic stimuli.[34] Further evidence of defective osmoreceptor function in a variety of disease states was presented by Robertson[1] in a recent review article. Our patients differ from most of those previously described as having upward "resetting of the osmostat" (i.e., a higher threshold for osmotic release of ADH than is normal) in that the latter had detectable hypothalamic lesions and a lack of thirst.[2,35,36]

Plasma ADH values were not necessary for making the diagnosis in the patients we studied, and, as shown by patient VII-13, they may not always be definitive, requiring correlation with the serum osmolality. We agree with Moses and associates[37] that measurement of the plasma ADH level provides useful confirmation but is essential for the diagnosis in only a small minority of patients. It is possible, however, that ADH assays, if reliably performed, may aid in further elucidating the pathogenesis of different forms of diabetes insipidus.

In conclusion, we have described a large kindred with hereditary central diabetes insipidus. The plasma ADH levels were low, as in the two other families so far for which these levels have been reported. The reason for this deficit, however, remains to be explained. The values found to date are too low to support the hypothesis of a simple deficit of ADH production. Other possibilities include anatomic involution of an area of the hypothalamus and, as hinted at in our patients, deficient functioning of the osmoreceptors. Further efforts to distinguish osmotic and volemic regulation of ADH secretion will be of interest in these cases.

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