CASE REPORTS

Vasopressin function in familial cranial diabetes insipidus

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Summary

A family suffering from cranial diabetes insipidus, that extends over 4 generations, is described. Inheritance of polyuria was autosomal dominant. Vasopressin function was studied in members of the last 2 generations, 4 of whom had polyuria. Osmoregulation of vasopressin secretion was assessed by infusion of hypertonic saline. Plasma vasopressin remained undetectable in one patient, while 2 others had very blunted vasopressin responses to osmotic stimulation. Three non-osmotic stimuli were applied. Controlled hypotension produced by trimetaphan infusion and insulin-induced hypoglycaemia did not increase plasma vasopressin but apomorphine-induced nausea caused a minimal rise in plasma vasopressin to 0.7 pg/ml. Polyuria and thirst resolved with antidiuretic therapy in all patients studied.

Congenital absence of vasopressin as in Brattleboro rats is unlikely to account for diabetes insipidus in this disorder since small increases in vasopressin have been demonstrated in these patients. In view of previous post-mortem findings, familial cranial diabetes insipidus is most likely to be due to degeneration of vasopressin-synthesizing neurones.

Introduction

The familial occurrence of cranial diabetes insipidus (CDI) is exceedingly rare, accounting for perhaps 1% of CDI. It was first recorded by La Combe in 1841, as quoted by Forssman (1945) and approximately 40 reports with family trees, the largest of which described 20 patients over 7 generations (Levinger and Escamilla, 1955), have subsequently appeared in the literature. In more recent years a familial syndrome of diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) and atonia of the urinary tract and bladder has been observed (Page, Asmal and Edwards, 1976; Cremers, Wijdeveld and Pinckers, 1977; Nagi, 1979). The mode of inheritance is different in the 2 types of familial CDI. It appears to be autosomal recessive in the familial syndrome of

DIDMOAD (Sunder *et al.*, 1972) but usually autosomal dominant in isolated CDI (Pender and Fraser, 1953).

The diagnosis of CDI in all cases so far reported has been based on indirect assessment of vasopressin function using urinary measurements during dehydration (Dashe *et al.*, 1963) or hypertonic saline infusion (Carter and Robbins, 1947). As yet, no attempt has been made to define vasopressin function more precisely in familial CDI.

The authors report their observations on vasopressin function assessed by plasma arginine vasopressin (AVP) response to osmotic (5% saline) and non-osmotic (hypotension, hypoglycaemia, and nausea) stimuli in a family suffering from CDI, which spans at least 4 generations and which shows autosomal dominant expression of the disease. Each stimulus applied in this study is believed to release AVP by an independent mechanism (Robertson, 1977; Baylis and Robertson, 1979).

Patients

The pedigree of the family is given in Fig. 1. The mother (R.H., identified by an asterisk in Fig. 1) was a 36-year-old Caucasian. She had been told by her parents that she had polyuria as an infant. She suffered intense thirst and polyuria throughout childhood. Results of investigation at the age of 20 years suggested CDI and she started treatment with i.m. injection of vasopressin tannate in oil. She was unable to tolerate the injections, so all antidiuretic therapy was stopped after 6 months' therapy. Enuresis continued until 8 years old. She remained without treatment for 25 years during which time thirst was her major complaint, drinking 0.5-1 litre each hr but she was also troubled by frequent nocturia. However she became accustomed to her symptoms. In 1973, thyrotoxicosis due to Graves' disease was diagnosed, and a partial thyroidectomy was performed. Three months after operation she developed hypothyroidism and thyroxine replacement therapy was started. At the time of her thyrotoxicosis, further investigations into the polyuria

were made. CDI was confirmed following dehydration tests and the demonstration of concentration urine after administration of aqueous vasopressin. She was treated with intranasal lysine vasopressin (3 times per day) which controlled thirst and day-time polyuria.

mother was a member of the 4th generation, who was reported to have a lifelong history of polyuria and thirst. She died, aged 56 years, from presumed diabetes mellitus. No other members of the family had diabetes mellitus or any other stigmata associated with the syndrome of CDI, diabetes mellitus, optic atrophy and deafness (Cremers *et al.*, 1977).

Examination of R.H. after stopping lysine vasopressin revealed a moderately obese woman (88.6 kg). She was not dehydrated. BP 160/75 mmHg, supine. There was a well healed thyroidectomy scar. She was clinically euthyroid and had no physical signs suggestive of hypopituitarism or other anterior pituitary disorders. Fundoscopy and visual fields were normal. Routine investigations showed a normal lateral skull X-ray, fasting serum glucose 4.9 mmol/l and serum sodium 139 mmol/l. Anterior pituitary assessment by insulin-induced hypoglycaemia revealed a 10-fold rise in serum growth hormone and a peak serum cortisol concentration of 750 nmol/l. Physical examination of the 4 children was normal.

Methods

Patients were studied after fasting overnight, but they were allowed free access to water. Smoking, alcohol and other beverages were not allowed. All medications including antidiuretic preparations had been discontinued 1 week before studies, except thyroid replacement therapy (patient R.H.). Urine output over 24 hr was measured.

The mother (R.H.) participated in 4 studies which assessed vasopressin response to osmotic stimulation and 3 independent non-osmotic stimuli. Osmoregulation of vasopressin was studied in the 2 elder polyuric children. The non-polyuric child had plasma AVP measured after overnight dehydration and the youngest child had one plasma AVP measurement when polyuric.

On the morning of dynamic studies, patients voided urine and were weighed before lying supine on a couch. Fluid was restricted thereafter. An aliquot of urine was taken to measure osmolality by the method of freezing-point depression (Advanced Instruments Inc., Osmometer Model 3R). A BP cuff with transducer was sited over the popliteal artery and attached to a semi-automatic BP recording device (Arteriosonde, Model 1216). BP was recorded at intervals of 2 min throughout the study. Two indwelling cannulae were introduced into ante-cubital veins, one for intermittent venous sampling and the other for infusion of drugs. Blood was drawn into chilled heparinized glass tubes and centrifuged at 4°C within 30 min of sampling to separate plasma from cells. A 2.5 ml aliquot was removed to measure plasma osmolality and glucose by an oxidase method (Beckman Glucose Analyzer,

FIG. 1. Pedigree of family. Members having CDI documented in present study are represented by filled symbols and those with a history of lifelong polyuria (2 dead) by stippled areas. * = the mother, R.H.

After an early marriage to a non-polyuric Caucasian, R.H. had 4 children. Her 4 pregnancies were unremarkable, and labour started spontaneously on each occasion. All deliveries were normal. The eldest child is a boy (15 years old) who has never suffered from polyuria, thirst or nocturia. The remaining 3 are girls (aged 13, 12 and 9 years), all of whom have had gross polyuria and thirst. Polyuria was first noted in these children between the ages of 6 weeks and 6 months. CDI was confirmed in these 3 children by the age of 2 years. After initial vasopressin therapy, they were changed to lysine vasopressin nasal spray. Previous symptoms of thirst and polyuria were then controlled in the children.

The father of R.H. also had a history of polyuria, nocturia and thirst from early childhood extending throughout his life until his death from a myocardial infarction when aged 42 years. At no time was he investigated or treated for polyuria. His sister was reported to have polyuria and thirst, but contact with her had been lost. The paternal grand-

Model 11L). The remaining plasma was deep frozen at -20°C to measure AVP by immunoassay (Robertson *et al.*, 1973).

Osmoregulation of vasopressin release was assessed by observing the plasma AVP response to the infusion of hypertonic saline (5%) at a rate of 0.06 ml/min/kg for 2 hr. Two 10-ml blood samples were taken before the start of the infusion, and samples were taken at 20 min thereafter for 2 hr. A further sample was collected 15 min after stopping the infusion. The time at which thirst was first experienced was noted.

The first of 3 non-osmotic stimuli (R.H. only) was applied 30 min after hypertonic saline infusion. Apomorphine (0.02 mg/kg) injected subcutaneously, induced severe nausea after 5 min. Blood was sampled at 5–10 min intervals for 30 min. On a separate occasion controlled hypotension was produced by infusion of trimetaphan (250 mg in 500 ml 5% dextrose) at a rate of 0.5 mg/min. The infusion rate was doubled at intervals of 10 min until a fall in mean arterial BP of about 35% had been achieved. Blood samples were drawn at 5–10 min intervals until adequate hypotension had occurred. Finally, symptomatic hypoglycaemia was induced by i.v. injection of soluble insulin (0.15 u./kg). Blood samples were drawn at 15–30-min intervals for 2 hr.

Results from similar studies performed in 11 healthy individuals (5 male), age range 20–32 years provided normal reference data. Informed consent was given, by each patient and parent where applicable, for studies which had been approved by the Human Research Ethical Committee, Indiana University Medical Center.

Results

The urine output of R.H. off antidiuretic medication ranged between 12–14 litres/24 hr. The polyuric daughter's urine output was 6–8 litres/24 hr. The son was not polyuric (urine volume < 1.5 litres/24 hr).

The results of hypertonic saline infusion are shown in Fig. 2. None of the 3 patients developed nausea/emesis or hypotension during saline infusion. Initial urine osmolalities were very low (R.H. 61; T.H. 77; K.H. 74 mmol/kg). Despite a considerable hypertonic stimulus and plasma osmolality rising by 34 mmol/kg, plasma AVP concentration of R.H. remained undetectable; T.H. had a minimal increase in plasma AVP to 0.6 pg/ml after an increase of plasma osmolality of 24 mmol/kg; although K.H. had low detectable values of plasma AVP throughout the infusion, the rise in plasma AVP was only 0.5 pg/ml. The relatively high plasma AVP value of K.H. was probably due to the presence of vasopressin antibodies in her serum. At a dilution of 1:100, her serum specifically bound approximately 20% of iodinated AVP, thus leading to a spuriously high

FIG. 2. Plasma AVP response to hypertonic saline infusion. The shaded area represents the normal response; LD = the limit of detection. Polyuric patients are shown by circles.

immunoreactive plasma AVP concentration. All patients experienced thirst during the infusion at plasma osmolalities (R.H. 299; T.H. 295; K.H. 299 mmol/kg) similar to normal (298.6 ± 3.6 mmol/kg mean $\pm$ s.d.). The youngest child, L.H., was dynamically tested, but her plasma AVP concentration was undetectable when she was polyuric and slightly dehydrated (plasma osmolality 293 mmol/kg). The son's values obtained after overnight dehydration fell within the normal range (Fig. 2).

Figure 3 shows the plasma vasopressin response to non-osmotic stimuli applied to R.H. Infusion of trimetaphan caused a 38% fall in mean arterial pressure but plasma AVP remained undetectable. Nausea induced by apomorphine resulted in a minimal increase of plasma AVP to 0.7 pg/ml associated with a slight fall in mean arterial pressure of 18%. There was no rise in plasma AVP despite profound hypoglycaemia (plasma glucose fell from 5.6 to 1.9 mmol/l).

After completion of the studies, all 4 patients were treated with the synthetic vasopressin analogue, DDAVP, which promptly and completely abolished the polyuria and polydipsia.

Discussion

A diagnosis of CDI could be confidently made in the 3 patients who were osmotically stimulated in view of the absent or grossly impaired plasma AVP responses to hypertonic saline in the presence of vasopressin-sensitive polyuria. No other abnormality of the pituitary was demonstrated. The youngest child had undetectable plasma AVP when plasma tonicity was slightly increased and polyuria was

present, suggesting CDI. The only son, however, had a normal response to overnight dehydration and did not suffer from polyuria. Thus, 3 of the 4 children had evidence of CDI.

Many of the non-osmotic stimuli to AVP release are extremely potent and those chosen to characterize the mother's vasopressin secretion are believed to act by independent mechanisms (Robertson, 1977; Baylis and Robertson, 1979). The mother showed no response to profound hypotension or hypoglycaemia and had a minimal response to severe nausea. It is therefore probable that her AVP reserve was extremely poor.

FIG. 3. Plasma AVP response to non-osmotic stimulation of R.H. (a) shows the results of trimetaphan infusion; (b) shows the plasma AVP response to apomorphine-induced nausea, and (c) the effect of insulin-induced hypoglycaemia. The shaded area represents the normal response; LD = the limit of detection. Severe nausea was experienced between 5 and 15 min after injection of apomorphine.

Unfortunately, the other members of the family reported to have polyuria were unable to be tested, but R.H. was able to give a clear description of the lifelong polyuria of her father. It would appear that polyuria probably extended over at least 4 generations. The mode of inheritance is autosomal

dominant, which agrees with the majority of other families reported (Weller, Elliott and Gusman, 1950; Pender and Fraser, 1953; Levinger and Escamilla, 1955; Moehlig and Schultz, 1955; Braverman, Mancini and McGoldrick, 1965). Sex-linked recessive inheritance of familial CDI has been described but appears to be very rare (Forssman, 1955).

Not all the affected members of this family are without measurable immunoreactive plasma AVP, although the AVP concentrations achieved after stimulation do remain low. These findings are in contrast to the animal model of familial CDI, the Brattleboro rat, which completely lacks the ability to synthesize AVP (Valtin, 1967). The defect in this strain of Long-Evans rat is transmitted by autosomal recessive inheritance. The precise defect in Brattleboro rats has yet to be determined, but it is likely to be an enzyme defect specific to AVP synthesis since the other neurohypophyseal hormone oxytocin is produced normally (Valtin, Sokol and Sunde, 1975). Consequently, the homozygous Brattleboro rat is polyuric from birth. The onset of polyuria in the members of this family dates from 6 weeks to 6 months, implying that the abnormality producing AVP deficiency is different from that in the Brattleboro rat. Further evidence to support this view comes from comparison of histological data from the hypothalamus and neurohypophysis of the Brattleboro rat and patients with autosomal dominant familial CDI. Although post-mortem reports are few in either idiopathic or familial CDI (Blotner, 1958; Braverman *et al.*, 1965), they agree upon a striking decrease in nerve cells of the supra-optic and paraventricular nuclei and a small neurohypophysis. In contrast, Brattleboro rats have a normal complement of nerve cells in these nuclei with a slightly enlarged neurohypophysis (Valtin, 1967). In view of these post-mortem findings it has been suggested that familial CDI is due to primary degeneration of the AVP-synthesizing neurones (Braverman *et al.*, 1965), which might also explain the delayed onset of polyuria after birth so often observed. Furthermore, the mode of inheritance differs between the human and animal types of hereditary CDI. Thus, it is most unlikely that this family represents a human expression of the rat disorder.

Nevertheless, the site of the defect in this family is probably quite discrete since the thirst mechanism, the centre of which is believed to be located in the anterior pre-optic hypothalamus (Robertson, 1979), remained intact. Also, there is some clinical evidence to suggest that oxytocin function was not deranged in R.H. because she delivered 4 children quite normally at a time when she was grossly polyuric. However, definite conclusions about oxytocin function cannot be drawn as formal tests were not performed. Furthermore, no anterior pituitary dysfunction was

observed in R.H. or her polyuric children. It would therefore appear that this family has a specific isolated defect of vasopressin function causing CDI inherited in autosomal dominant manner.

Acknowledgments

We wish to thank Dr R. Dexter for allowing us to study his patient R.H., and we express our gratitude to Miss M. B. Gaskill and Miss J. Musselman for technical assistance. P.H.B. was in receipt of a Fulbright-Hays Travel Scholarship. The work was supported by the Veteran's Administration and a grant from the NIH No. ROI AM-21102.

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