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Congenital Nephrogenic Diabetes Insipidus with Bilateal Hydronephrosis : Indomethacin in Treatment of Nephrogenic Diabetes Insipidus

Young Mo Sohn, Chul Lee, Pyung-Kil Kim and Duk Jin Yun

Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea

A 13-year-old boy was diagnosed as having primary nephrogenic diabetes insipidus, and symptoms developed at 3 years of age. Subsequently he developed bilateral hydronephrosis and a neurogenic bladder. His pedigree could be explored back 5 generations and represented an inheritance as an X - linked recessive transmission factor. He was treated with indomethacin 2 mg/kg/day plus chlorothiazide 500 mg/day and this new treatment showed a markedly decreased urine output and increased urine osmolarity. (Nephrogenic diabetes insipidus, Hydronephrosis, Indomethacin)

Diabetes insipidus is a rare disease, characterized by polyuria and polydipsia, and results from lack of the antidiuretic hormone, arginine vasopressin. Nephrogenic diabetes insipidus is an hereditary disorder of the kidney characterized by insensitivity to the antidiuretic action of vasopressin (Waring *et al,* 1956). Evidence for the current belief that vasopressin is present in this disorder but that the nephron cannot respond to it has been summarized by Orloff and Burg (Orloff *et al,* 1966). Recent studies indicate the usefulness of ethacrynic acid (Brown *et al,* 1966), cyclic AMP (Jones *et al,* 1972) and indomethacin (Bladhar *et al,* 1978). We have observed a case of congenital nephrogenic diabetes insipidus with bilateral hydronephrosis and represented an X - linked recessive transmission inheritance. He was treated with indomethacin and chlorothiazide and this new treatment showed a markedly decreased urine output and an increased urine osmolarity.

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CASE REPORT

First Admission

A 7-year-old boy was admitted to Severance Hospital because of polydypsia (about 5 liters per day) and polyuria. He was well until about 3 years of age, when he began to complain of excessive thirst and drink large amounts of water with frequent voiding. His birth weight was 4.3 Kg and there was no birth trauma history. But when he was 3 years old, he was admitted to a private clinic due to fever of unknown origin and loss of appetite. After discharge, he developed thirst and drank excessively with frequent voiding at 30 minute intervals for the next 4 years. But no specific evaluation and treatment of this problem were done. There were many family members on the maternal side who had polyuria and polydypasia. But most of them were not studied for etiology. On admission, vital signs were normal including

blood pressure. Physical examination revealed no abnormalities. Neurological examination was negative. Fundoscopic findings were normal. The hematocrit was 35%; the hemoglobin was 11.6 g per 100 ml. The white blood cell count was 6,400 per cubic mm with 78% neutrophils, 21% lymphocytes. The urinalysis was normal except specific gravity 1,002. Water deprivation test and Hickey Hare test were performed with positive response. Pitressin test gave an unresponsive output. An X-ray film of the chest and skull were normal. Bone age corresponded to about 6 to 7 years of age without evidence of retardation. An intravenous pyelogram revealed a neurogenic bladder with probable reflux. He was discharged without treatment and his problem was not resolved.

Second Admission

He was re-admitted at 13 years of age to this hospital because of the same problems plus one of micturition. He appeared thin, and chronically ill looking. He was not treated but from about one year ago, he developed nocturnal enuresis and he was treated with Persamine (Imipramine Hydrochloride) at a local clinic for a few month's benefit it. He still drinks water 6-7 liters per day. On physical examination, the skin was not dry and the tongue was not coated. The heart and lungs were normal. The abdomen was normal without organomegaly. The external genitalia was normal for his age. Neurological examination was normal. The hematocrit was 33%; the hemoglobin was 11.7 g/dl. The white blood cell count was 10,500 per cubic mm, with 71% neutrophils. The serum osmolarity was 132 mOsm/L. There was 10.5 mg/dl, inorganic phosphrous was 4.3 mg/dl, BUN was 30.4 mg/dl, uric acid was 8 mg/dl, total protein was 6.3 g/dl, albumin was 4 g/dl, creatinine was 1.2 mg/dl. The urine sodium was 142 mEq/L, potassium was 4.6 mEq/L and the CO_2 content was 23 mM/L. An X-ray film of the chest and skull were normal. An intravenous pyelogram revealed a marked hydronephrosis bilaterally and a neurogenic bladder. A voiding cystourethrogram revealed no reflux. The cystometry revelaed a lower motor neuron type neurogenic bladder. Water deprivation test and Pitressin test were performed (Table 1).

Table 1. Water deprivation test

Time	Serum (mOsm)	Urine (mOsm)	Urine S.G.*
6:00 A.M.	288	151	1.002
7:00		151	1.003
8:00		149	1.005
9:00	316	118	1.002
10:00		108	1.002
11:00		108	1.002
12:00		151	1.002
1:00 P.M.**		108	1.002
1:00		151	1.003

* Specific Gravity
** Pitressin administered

Table 2. Urine volume and serum osmolarity after treatment

	Volume (ml/24 hrs)	Osmolarity (mOsm/kg)
Control period (no treatment)	5,800	108
1st 5 days after treatment	4,100	159
2nd 5 days	3,100	142
3rd 5 days	2,500	306
4th 5 days	2,000	253
weekly 2,000	2,000	151
weekly	2,200	146
weekly	*	156
weekly	*	153
weekly	*	145

* Under 2,000 ml/24 hrs

He was treated with indomethacin 2 mg/kg/day and chlorothiazide 500 mg/day. The following

table shows urine volume and serum osmolarity after treatment.

DISCUSSION

Diabetes insipidus, an inability to maximally concentrate the urine, is associated with polyuria and polydipsia which results from the lack of the antidiuretic hormone, arginine vasopressin or the inability of the kidney to respond to either endogenous of exogenous ADH caused by various factors which may include the following; (1) the walls of the distal convoluted tubule and collecting duct are unable to increase their is no osmotic gradient between the tubular urine and the interstitial fluid surrounding the distal segments of the nephron due to so-called washout or renal medullary solutes; and (3) possibly, a combination of the factors (Dousa, 1974).

Diabetes insipidus may result from any condition which damages the neurohypophysical system. Randall *et al.* have suggested an etiologic classification of this condition with two major categories: primary and secondary diabetes insipidus (Blotner, 1958). The primary diabetes insipidus includes familial and idiopathic type. The secondary diabetes insipidus results from head trauma (accidental or neurosurgical) and neoplasms (primary or metastatic). Other etiologic factors are metastatic breast cancer, sarcoidosis, birth injuries, eosinophilic granuloma and a variety of local infections of the brain.

The idiopathic type constitute the major group, comprising 45 per cent of the total in Blotner's series (Blotner, 1958), and may become manifest at any age and affect either sex. On the other hand, familial diabetes insipidus is uncommon and must constitute less than 1 per cent of paitents with diabetes insipidus and may occur in infancy or childhood and may affect either sex.

Primary nephrogenic diabetes insipidus is believed to have a sex-linked recessive mode of inheritance (Forssman, 1975). It affects male subjects primarily and rarely occurs in femals subjects. The Hopewell hypothesis subjects that most patients in North America are descendants of Ulster Scot, who settled in Nova Scotia in the 18th Century (Bond and Crawford, 1969). Rare instances of authentic nephrogenic diabetes insipidus have been encountered with no evidence of affected relatives, suggesting new mutations (Gardner, 1975; Feigin *et al,* 1970; Kaplan *et al,* 1959). In 1947 Williams and Henry introduced the term "nephrogenic" to describe a form of diabetes insipidus in patients whose symptoms were not relieved by the administration of vasopressin. The disease had been mentioned in 1923 by Veil, who noted the same lack of response in some of his patients (Kaplan *et al,* 1959).

The basis for the failure to respond to vasopressin is unknown. There is evidence that vasopressin influences the metabolism of the renal medulla in vivo (Jones and Welt, 1967). Vasopressin in believed to act at the cellular level by increasing the formation of adenosine 3.5, cyclic monophosphate, which then increases epithelial permeability. Both cyclic-AMP and vasopressin increase the epithelial permeability to water and stimulate active sodium transport in the isolated toad bladder (Orloff and Handler, 1962; Edelman *et al,* 1964). Both substances increase the permeability to water of isolated collecting tubules (Grantham and Burg, 1966). The concentration of cyclic-AMP in toad bladder cells is increased by vasopressin, and this hormone also stimulates production of cyclic-AMP by homogenates of dog kidney (Handler *et al,* 1965); Brown *et al,* 1963). Cyclic-AMP is present in human urine (Butcner and Sutherland, 1962) and its excretion may increase in response to vasopressin (Pawlson *et al,* 1970). Moreover,

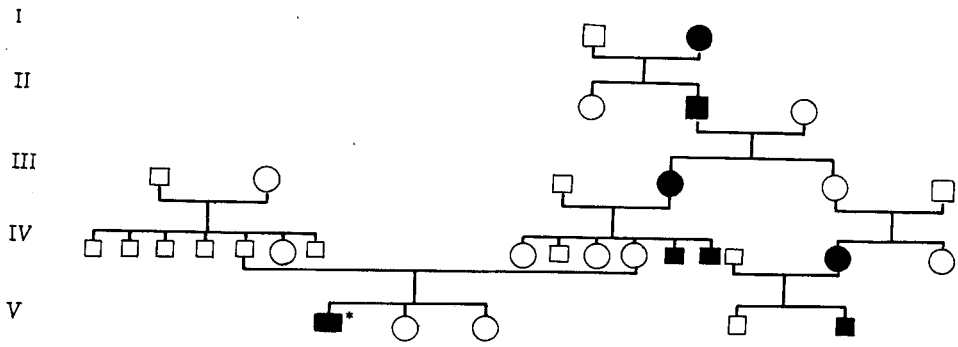

Fig. 1. Pedigree representing nephrogenic diabetes insipidus, inherited as a recessive, X chromosome – linked trait and variable prevalence of female heterozygous.

* Probend □ Unaffected male ■ Affected male
○ Unaffected female ● Affected female

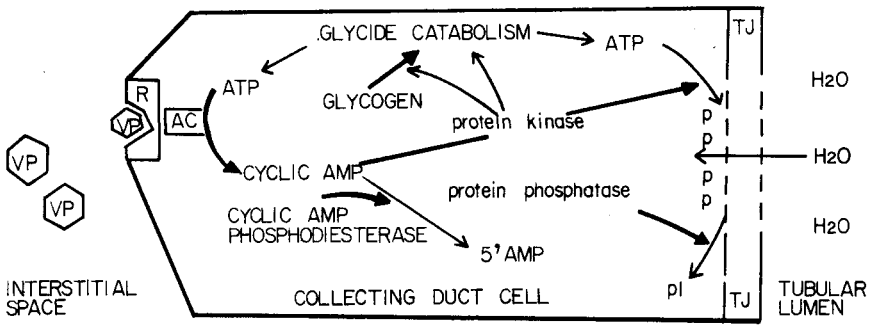

Fig. 2. Current scheme of mechanism of action of ADH on the cell of the collecting duct of the mammalian nephron. VP=vasopressin; AC=adenyl cyclase; R=receptor for vasopressin; TJ= tight junction.

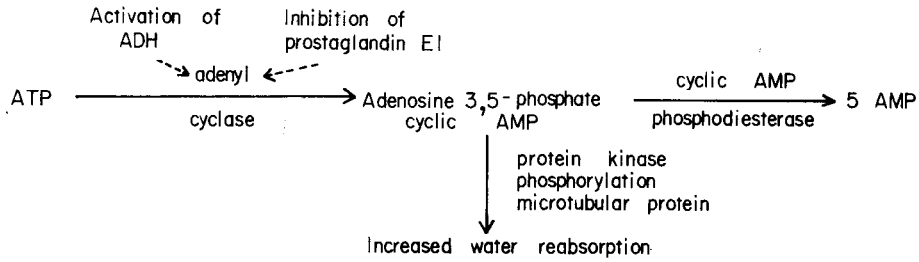

Fig. 3. Mechanism of action of prostaglandin E_1 on the collecting duct of the nephron

the administration of cyclic-AMP causes antidiuresis (Levin, 1968; Barraclough and Jones, 1970). There is thus considerable evidence that vasopressin's action on the kidney is mediated by cyclic-AMP. It is possible that in nephrogenic diabetes insipidus the defect at the cellular level involves a failure to generate cyclic-AMP in response to vasopressin.

The basis of the action of ADH on tubular cells of the distal nephron is that the ADH

molecule does not enter into the cell but interacts on the cell surface with a specific receptor. Hormon-receptor interaction leads to production of cyclic adenosine -3′,5′-monophosphate which serves as an intercellular mediator of ADH and directly or indirectly induces the ultimate functional change, the increase in water permeability of the tubular epithelium. The cellular mechanism of ADH action involves two complexes: (1) ADH – induced cyclic AMP synthesis and (2) cyclic AMP – induced permeability change. The first step in the action of ADH involves binding on specific ADH receptors located on the outer surface of the cell membrane. The specific localization of ^{131}I-labled ADH in the distal convoluted tubule and collecting ducts has been studied by autoradiographic techniques.

The ADH receptor in the cell membrane is associated with adenyl cyclase, an enzyme catalyzing the formation of cyclic AMP from adenosine triphosphate. The receptor is located on the outer surface of the cell membrane and the adenylate cyclase, or at least its catalytic site, is in contact with the cell interior. For convenience, the whole complex of ADH receptor and adenylate cyclase within the cell membrane is called the "ADH – stimulated adenylate cyclase." (Dousa, 1974). Cyclic AMP is converted to 5′-AMP by the enzyme, cyclic AMP phosphodiesterase. Cyclic AMP phospodiesterase is not influenced by ADH, and it probably plays an important role in the cyclic AMP metabolism of the distal nephron. Inhibitors of cyclic AMP phosphodiesterase, theophylline or aminophylline, or chlorpropamide can potentiate the effect of ADH or of exogenous cyclic AMP on renal tubules, probably by inhibiting cyclic AMP breakdown. The membrane permeability and other properties might be regulated by phosphorylation of specific membrane proteins controlling the permeability function of the luminal cell membranes. Major components of this phosphorylating system include luminal cell membranes. Major components of this phosphorylating system include (1) protein kinase, an enzyme that catalyze the transfer of gamma phosphorous from ATP to serine or threonine residues of polypeptidases and that is stimulated by cyclic AMP, (2) protein substrate supposedly located in the luminal cell membrane, and (3) protein phosphate, which catalyze the dephosphoryla-

Table 3. Etiologic factors of acquired nephrogenic diabetes insipidus

Drugs
Lithium
Tetracyclines
Methoxyflurane
Sulfonylureas
Diatrizoate toxicity at arteriography
Propoxyphen
Analgesic nephropathy
Sickle cell anemia
Hypopotassemia
Hypercalcemia
Chronic uremia nephropathy
Obstructive uropathy
Posterior urethral valves
Benign prostatic hypertrophy
Retroperitoneal fibrosis
Chronic pyelitis
Amyloidosis
Sarcoidosis

This patient's pedigree could be explored back 5 generations and represented inheritance as a X – linked recessive transmission factor (Fig. 1), which was acquired by his mother who was very intelligent, and whose brother was a doctor. In pedigree, only the maternal side was affected and represented variable prevalance of heterozygous female. Although other affected patients were not confirmed except this patient, this pedigree was much convincing evidence.

tion of cell proteins (Dausa *et al*, 1972). ADH and cyclic AMP also through stimulation of phosphorylation of enzyme molecules by a cyclic AMP – dependent protein kinase, as in analogous systems from liver or muscle. Although the basic components of the proposed protein phosphorylating system have been found in mammalian renal medula and the effects of ADH and cyclic AMP on protein phosphorylation have been found in amphibian urinary bladder, this mechanism is still hypothetical (Dausa, 1974). Scheme of mechanism of action of ADH is summarized in Figure 2.

In vitro and in vivo studies show enhancement of ADH antidiuretic effect following inhibition of prostaglandin synthesis.

The secondary or acquired type of nephrogenic diabetes insipidus has been related to the following factors. (Table 3)

Nephrogenic diabetes insipidus is present at birth, though the diagnosis is frequently not made for several months. Frequent urination of a large volume of dilute urine, extreme thirst, repeated episodes of dehydration, and failure to thrive are the common initial manifestations. Frequent bouts of hypertonic dehydration with convulsions account for the observed mental retardation (Shapiro *et al*, 1978). Hydronephrosis has been reported in diabetes insipidus. The cause of the hydronephrosis is speculative, although polyuria alone seems to be the primary factor. When urinary volume per unit of time exceeds the capabilities of the ureter, dilatation occurs. Theoretically, the dilatation could result in ureteral decompensation and renal deterioration owing to hydronephrotic atrophy. Neurogenic bladder was also frequently found in diabetes insipidus and diabetes mellitus. The bladder was not responsive to chronic overflowing of urine.

There is no specific treatment of nephrogenic diabetes insipidus. Recently, ethacrynic acid (Brown *et al*, 1966) chlorothiazide (Crawford *et al*, 1959) and cyclic AMP (Jones *et al*, 1972) have been used. Blach *et al* (1978) have suggested that indomethacin and aspirin inhibit prostaglandin synthesis and thus enhance cyclic AMP – mediated ADH action, and indomethacin more strongly than aspirin. Aminophylline inhibits phosphodiesterase, thus increasing cyclic AMP. Chlorothiazide reduces extracellular volume and enhances proximal tubular fluid reabsorption. Ihibition of prostaglandin synthesis by indomethacin was an effective mode of treatment and was even more efficacious when indomethacin was combined with chlorothiazide. This patient was treated with indomethacin 2 mg/Kg/day plus chlorothiazide 500 mg/day and this new treatment showed a markedly decreased urine output and an increased urine osmolarity (Table 2).

REFERENCES

Barraclough MA, Jones NF: *Effects of adenosine 3',5'-monophosphate on renal function in the rabbit. Br J Pharm 40:334, 1970*

Bladhar Y, Zadic Z, Shermesh M, Goldin N, Barak Y and Levin S: *Prostaglandin synthesis inhibition in the treatment of nephrogenic diabetes insipidus. Abstract from international congress of nephrology. 1978 Montriol Canada*

Blotner H: *Primary or idiopathic diabetes insipidus; a system disease. Metabolism 7:191, 1958*

Bode HH, Crawford JD: *Nephrogenic diabetes insipides in North America – the Hopewell hypothesis. New Engl J Med 280:750, 1969*

Brown E, Clarke DL, Roux V, Sherman GH: *The stimulation of adenosine 3',5'-monophosphate production by antidiuretic factors. J Biol Chem 238: 852, 1963*

Brown DM, Reynolds JW, Michael AF, Ulstrom RA: *The use and mode of action of ethacrynic acid in nephrogenic diabetes insipidus. Pediatrics 37:477, 1966*

Boucher RW, Sutherland EW: *Adenosine 3',5'-pho-*

sphate in biological materials. I. Purification and properties of cyclic 3',5'-nucleotide phosphodiesterase and use of this enzyme to characterized adenosine 3',5'-phosphate in human urine. J Biol Chem 237:1244, 1962

Crawford JD, Kennedy GC: *Chlorothiazide in diabetes insipidus. Nature 183:891, 1959*

Dousa TP: *Cellular action of antidiuretic hormone in nephrogenic diabetes insipidus. Mayo Clin Proc 49:188, 1974*

Dousa TP, Sands H, Hechter O: *Cyclic AMP-dependent reversible phosphorylation of renal medullary plasma membrane protein. Endocrinology 91:757, 1972*

Edelman IS, Petersen MJ, Gulyassy PF: *Kinetic analysis of the antidiuretic action of vasopressin and adenosine-3',5'-monophosphate. J Clin Inv 43:2185, 1964*

Feigin RD, Rimoin DL, Kaufman RL: *Nephrogenic diabetes insipidus in a Negro kindrid. Am J Dis Child 120:64, 1970*

Forssman H: *The recognition of nephrogenic diabetes insipidus. A very small age from the history of medicine. Acta Med Scand 197:1, 1975*

Gardner LI: *Endocrine and genetic diseases of childhood and adolescence 2nd ed. Philadelphia: WB Saunders Co 1975 p 177ff*

Grantham JJ, Burg MB: *Effect of vasopressin and cyclic-AMP on permeability of isolated collecting tubules. Am J Physiol 211:255, 1966*

Handle JS, Butcher RW, Sutherland EW, Orloff J: *The effect of vasopressin and of theophylline on the concentration of adenosine 3',5'-phosphate in the urinary bladder of the toad. J Biol Chem 240:4524, 1965*

Handler JS, Orloff J: *Activation of phosphorylase in toad bladder and mammalian kidney by antidiuretic hormone. Am J Physiol 205:298, 1963*

Jones NF, Barraclough MA, Barnes N, Cottom DG: *Nephrogenic diabetes insipidus. Arch Dis Child 47:794, 1972*

Jones NF, Welt LG: *Adenosine triphosphate in rat renal papilla; effects of vasopressin and of ischemia. Am J Physiol 212:939, 1967*

Kaplan SA, Yuceoplu AM, Strauss J: *Vasopressin resistant diabetes insipidus. Am J Dis Child 97:308, 1959*

Levine RA: *Antidiuretic responses to exogenous adenosine 3',5'-monophosphate in man. Clinical Science 34:253, 1968*

Orloff J, Handler JS: *The similarity of effects of vasopressin on renal cyclic-AMP generation inpotassium deficiency and patients with sickle hemoglobin. Metabolism 19:694, 1970*

Shapiro SR, Woerner S, Adelman RD, Palmer JM: *Diabetes insipidus and hydronephrosis. J Urol 119:715, 1978*

Waring AJ, Kajdi L, Tappan V: *Congenital defect of water metabolism. Am J Dis Child 69:323, 1945*