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□ Case Report □

A Case of Congenital Nephrogenic Diabetes Insipidus Confirmed by Gene Analysis

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Nephrogenic diabetes insipidus (NDI) is a disorder in which the secretion of antidiuretic hormone is normal, but the response of the renal collecting tubules to vasopressin is impaired. Compared with acquired NDI (a-NDI), which is secondary to chronic bilateral incomplete urinary tract obstruction with hydronephrosis, congenital NDI (c-NDI) is a very rare heritable disorder that usually follows the X- linked recessive pattern. Clinical symptoms of c-NDI can be non specific, and often the disease ultimately results in failure to thrive, or mental retardation. Recently, the diagnosis can be confirmed by direct sequencing analysis of the peripheral blood specimens. The long-term results of treatment for c-NDI are not satisfactory. Reports on the follow up of c-NDI cases are rare and there is no report on the cases treated with combinations of three drugs. We report herein a case of severe c-NDI in an 8 year-old-boy with a severely dysconfigurated urinary tract system. The patient and his mother showed a frameshift mutation on the AVPR2 gene on chromosome Xq28:.847_851delTGCTG (p.C283fsX90). The patient showed normal growth and development by treatment with combinations of hydrochlorothiazide (65 mg/m^2), amiloride (0.3 mg/kg/d) and indomethacin (100 mg/m^2), yet after five years he needed adjuvant cystostomy to relieve him from the residual symptoms of urgency with polyuria. **(Korean J Pediatr 2005;48:669-674)**

Key Words : Nephrogenic diabetes insipidus (NDI), Congenital, AVPR2

Introduction

Nephrogenic diabetes insipidus (NDI) is a rare disorder caused by the insensibility of the collecting tubules to normally secreted antidiuretic hormone (ADH), and this causes the failure of the normal antidiuretic response. NDI can be either congenital or acquired. The defect in NDI has suspected to be located at any of the steps from the binding of antidiuretic hormone to the renal V2 receptors (AVPR2) to the generation of c-AMP and the reabsorption of water[1]. Since the previous report by Forssman[2], several cases in adult patients have been reported. A Korean case of congenital NDI (c-NDI) has been reported on by Sohn et al.[3] and a Korean case of acquired NDI (a-NDI) has been reported on by Suh et al.[4], but pediatric cases of NDI have rarely been reported.

The majority of the cases of c-NDI follow the X-linked recessive pattern and they are explained by mutations in the arginine vasopressin receptor gene (AVPR2), which codes for vasopressin type-2 (V2) receptor in region of Xq28[5-7]. However, cases of partial NDI that follow the autosomal recessive pattern with defects of the aquaporin-2 receptor (AQP2) of the water channel have also been reported[8, 9]. a-NDI is suspected to have a poor response to ADH due to the compromised function of the aquaporin-2 gene[10]. Acquired cases are largely caused by vesicoureteral reflux (VUR) with obstructive lesions at the posterior urethral valve in children, and by tumor or several drug reactions in aduls[11, 12].

Diagnosis of NDI can be made by the failure to concentrate urine after a challenge with hypertonic saline and vasopressin. c-NDI can be diagnosed by a family history of inheritance. Dozens of mutations of the AVPR2 gene have recently been shown, and diagnosis can be confirmed by direct sequencing analysis of the peripheral blood specimens.

Previously, there was no curative treatment for patients with c-NDI, so it was important to exclude a-NDI as this disease could be improved by removing the underlying

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causes. There have been many challenges for the treatment of c-NDI with diuretics and non-steroidal anti-inflammatory agents as the mainstays of treatment, but the long term results of such treatment have not been satisfactory. To date, reports on the long term follow up results of treatment for c-NDI and the related complications are very rare, and there have been no reports on these cases that were treated with combinations of three drugs.

We report herein report on the five-year-follow up of a case of X-linked recessive c-NDI having a non-obstructive severely dilatated urinary tract system. The patient partially improved with chlorothiazide, amiloride and indomethacin, and the patient ultimately needed adjuvant percutaneous cystostomy.

Case Report

A 8-year old boy was transferred from the urologic department to the pediatric department for the evaluation of his renal function. He was in a suprapubic cystostomy state due to the huge volume of polyuria, which was over 12 liters a day. He showed agitation and craving for water. His polyuria had continued for over 4 years and his uncle in law suffered from mental retardation (Fig. 1). He was 124 cm tall (25-50 percentile) and weighed 22 kg (25-50 percentile). His systolic blood pressure was 100 mmHg, and the diastolic pressure was 60 mmHg, his pulse rate was 118/min, the respiration rate was 32/min and his body temperature was 38.9℃. Laboratory findings showed the following results : blood urea nitrogen 4.8 mg/dL, creatinine 1.5 mg/dL, sodium 139 mEq/L, potassium 4.4 mEq/L, hemoglobin 10.6 g/dL, hematocrit 30% and WBC 11.800/mm^3. Urinalysis showed a specific gravity of 1.000 and 5-9 WBC/HPF microscopically. The plasma osmolality was 280 mOsm/kg and the urine osmolality was 37 mOs/kg. The serum ADH level was 24.79 pg/mL (normal range 0.6-6.7 pg/mL). The glomerular filtration rate (GFR) was within normal limits. Under the impression of diabetus insipidus, we performed a water deprivation test and a vassopressin stimulation test. Not withstanding the water restriction (the serum osmolality was from 280 to 285 mOsm/kg) his urine specimen did not shown any changes in specific gravity and osmolality (41 mOsm/kg). Challenge with transnasal disaminoarginine vasopressin (DDAVP) also failed to concentrate the urine in which the osmolality of urine was above that of plasma 2 hours after administration of DDAVP, the serum osmolality was 275 mOsm/kg H_2O and the urine osmolality was 175 mOsm/kg H_2O (Table 1). The serum AVP level after water deprivation was above the normal range (22.95 pmol/L) (Fig. 2). *Pseudomonas aeruginosa* was grown on the urine culture. Abdominal sonogram showed bilateral severe hydronephrosis (Fig. 3A). The voiding cystourethrogram (VCUG) and intravenous pyelogram (IVP) showed the typical christmas-tree appearance of the dysconfigurated huge bladder with vesicoureteral reflux (VUR) of grade III (Fig. 3B). No obstuctive lesion was suspected. Dimercaptosuccinic acid (DMSA) renal scan showed cold spots on the upper pole of both

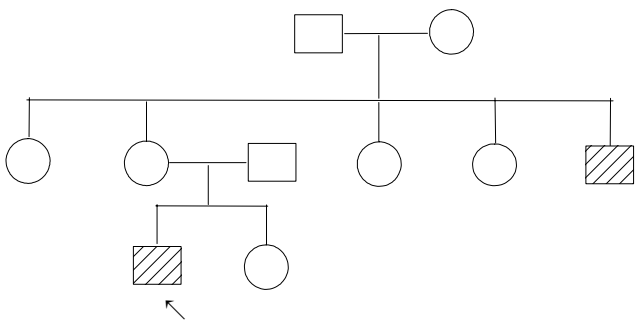

Fig. 1. Pedigree of the patient's family shows the X-linked recessive trait (arrow : patient, hatched square : man with diabetes insipidus).

Table 1. Patient's Laboratory Findings after the Water Deprivation Test that Followed 20 ug of DDAVP Administration Intranasally

	Water deprivation test		After challenging with DDAVP*	After thiazide & amiloride	
	Before	After		Before water deprivation	After water deprivation
Urinary Specific Gravity	1.000	1.000	1.010	1.005	1.010
Urine Osmolality (mOsm/kg H_2O)	37	41	175	99	175
Serum Osmolality (mOsm/kg)	280	285	275	254	277
Daily Volume of Urine (mL/day)	12000			4000	

*DDAVP : 1-desamino-8-D-arginine vasopressin

kidneys. On the urodynamic study, neurogenic bladder was suspected. The brain MRI showed no organic lesion. After treatment with hydrochlorothiazide (65 mg/m^2) and amiloride, the urine volume was reduced from 12 liters to 4 liters a day. Those drugs were successful in reducing urine volume, but they failed to increase the urine osmolality above the plasmal level. However, we failed to reduce the urine volume further with combinations of hydrochlorothiazide and amiloride or with hydrochlorothiazide and indomethacin. The urine osmolality could not be increased over 200 mOsm/kg. His enuresis still continued and he suffered from distraction due to urgency during the day time at school. Oral DDAVP and oxybutinin as anticholinergics were added to treat the neurogenic bladder. Follow up renal sonogram and IVP showed little interval changes of dysconfigurated urinary tract system (Fig. 4). He received cystostomy and the application of a urine collecting bag, which relieved him from the symptoms of urgency. Direct sequencing analysis of the peripheral blood specimen of the patient and his mother identified a frameshift mutation of the AVPR2 gene on chromosome Xq28:c.847_851delTGCTG (p.C283fsX90).

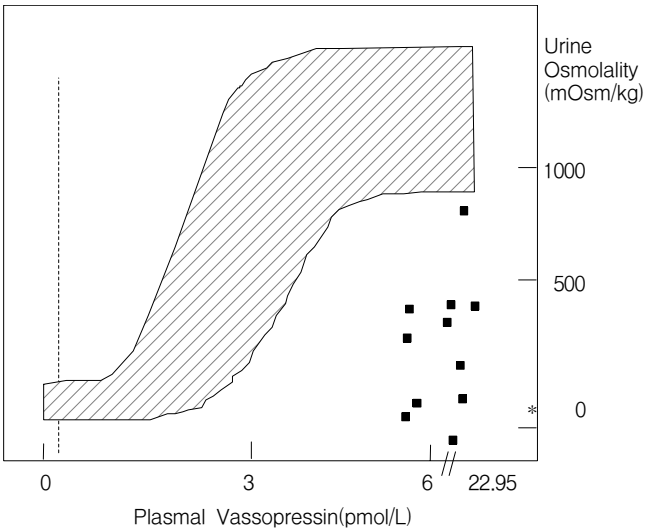

Fig. 2. Graph of the plasmal vassopressin level after water deprivation test; Normal and central DI patients are distributed on the hatched area of the graph and NDI patients are scattered far from the hatched area shown as a solid square. The index patient is showed as an asterix.

Discussion

Binding of vassopressin to the renal type V2 receptor on the basolateral membrane of the principle collecting duct cells results in the activation and generation of c-AMP and the resorption of water occurs across the apical membrane of collecting duct cells. Molecular studies of NDI have identified a number of genetic mutations or deletions of the gene that encodes for the antidiuretic (vassopressin V2) receptor located on Xq28. As c-NDI follows the X-linked recessive pattern in most cases, the predominant symptoms are usually found in males, but a heterogygote female can show a partial defect for the concentration of urine. The vassopressin V2 receptor is a classical 7-domain transmembrane protein, and genetic abnormalities have been located in the transmembrane domain as well as the external and internal segments of the receptor[13, 14].

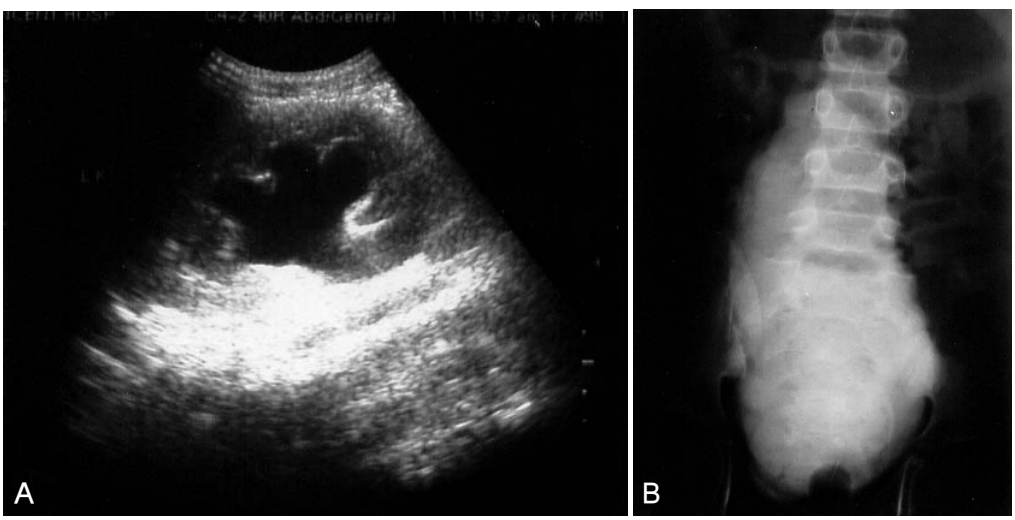

Fig. 3. (A) Sonogram shows hydronephrosis. **(B)** Voiding cystourethrogram shows christmas tree appearance of the dysconfigurated bladder.

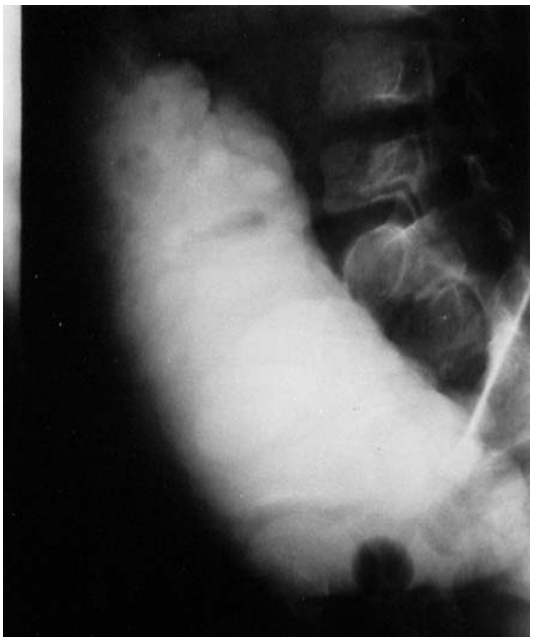

Fig. 4. Intravenous pyelogram shows little interval changes after treatment.

Another form of NDI that is due to genetic abnormalities of the water channel protein, aquaporin-2, has been described[8, 15]. Our patient was initially diagnosed with c-NDI only because of the clinical findings and familial history, and he was treated for five years until we confirmed the frameshift mutation on the AVPR2 gene on chromosome Xq28 by direct sequencing blood analysis of our patient and his mother.

As the symptoms of NDI can be non-specific in neonates and young infants, a high index of suspicion is important. Carefully history taking of improved irritability when giving water instead of formular feeding, the amount of daily intake and output, and a family history of DI or mental retardation can be critical clues for achieving a correct diagnosis. This disease can ultimately result in failure to thrive or mental retardation regardless of any efforts to treat it or in those cases with poor compliance to treatment[16, 17]. It is interesting that our patient had not shown hypernatremia or failure to thrive in spite of his severe diuresis of over 12 liters a day for 8 years. His body weight and height was estimated to be within the normal Korean range. A study on the clinical presentation and follow up of 30 patients with c-NDI showed that most of the patients were diagnosed within the first 2.5 years of life and most of them were on hydrochlorothiazide and amiloride treatment without significant side effects. Two patients suffered from severe hydronephrosis with rupture of urinary tract system after minor trauma[18]. The researchers reported that except for a possible milder phenotype in patients with a G185C mutation, no clear relationship between the clinical and genetic data could be found.

For the diagnosis, the purpose of water deprivation testing is to increase the plasma osmolality to the point that is usually associated with the sufficient release of ADH from the neurohypophysis to induce urinary concentration. After the increment in plasma osmolality to >10 mOsm/L, if the urine is still diluted, the patient has either central or nephrogenic diabetes insipidus (DI). DDAVP (l-desamino-8-D-arginine vasopressin) can then be used as a challenge test (intranasally 10 ug for infants, 20 ug for children or intravenously 0.08 ug/kg). Patients who have NDI do not increase their urine osmolality upon challenge with vasopressin, which remain below 200 mOsm/kg water[19, 20]. Discrimination of NDI from central DI can be also made by titrating the concentration of the plasma vassopressin (AVP) level. In NDI, the plasma vassopressin levels are normal or increased. After infusion of hyperosmolar saline (855 mmol/L) or after water deprivation testing, the concentration of AVP for patient with NDI is distributed far from that of the normal or central DI patient, and the AVP level of our patient was plotted in the NDI distribution area (Fig. 2).

As sodium and urea leads to renal water loss, for the treatment of NDI, restrictions of sodium to 0.7 mEq/kg/day and protein to 1 g/kg/day are very important. Some drugs are favored including hydrochlorothiazide and non-steroidal anti-inflammatory agents. The combination of hydrochlorothiazide (65 mg/m^2) and indomethacin (100 mg/m^2) is frequently used[21, 22]. Hydrochlorothiazide (3 mg/kg/d) can reduce urine output by 40% in infants[15, 23]. Hydrochlorothiazide interferes with sodium chloride absorption in the distal portion of the nephron; in NDI the resulting sodium depletion enhances the absorption of isoosmotic fluid in the proximal nephron and so reduces urine volume by decreasing the fluid delivered to the distal nephron. Thiazide commonly causes hypokalemia, which may further aggravate the concentration defect. Without sodium restriction, the good effects of thiazide cannot be achieved, and caution is needed not to increase the plasma uric acid level over 10 mg/dL. These patients may need to be administered a potassium-sparing agent such as amiloride (0.3 mg/kg/d)[15, 24]. Indomethacin, a prostaglandin synthetase inhibitor, pro-

bably decreases the renal blood flow and consequently increases water and electrolyte absorption in proximal tubules it also increases sodium absorption in the thick medullary ascending limb of Henle, with the consequent increase in the osmolar gradient of the contercurrent multiplier system[21]. It is important to consider the adverse effects of indomethacin; it may be used with an agent such as misoprostol, which is a prostaglandin analog, to reduce the risk of gastrointestinal ulceration[15]. Some patients with mutations of AVPR2 show a poor response to ADH, for which a combination of the above drugs with desmopressin achieves a better result[15]. The addition of a high dose of desmopressin to the combination of thiazide and indomethacin may reduce urine output still further. It is essential that all these patients drink adequate fluid volumes to quench their thirst. In the eighties, Sohn et al. have reported on a case that was improved by indomethacin[3]. Yet the patient in our case showed partial improvement to all the treatment modalities including a combination of hydrochlorothiazide and amiloride and also a combination of hydrochlorothiazide and indomethacin. For several months with hydrochlorothiazide and amiloride, the urine volume was reduced from 12 litter to 4.5 liters a day, but further reduction could not achieved by combination of hydrochlorothiazide and amiloride or with hydrochlorothiazide and indomethacin. His urine osmolality did not increase over 200 mOsm/kg. His enuresis continued and he suffered from distraction with symptoms of urgency during day time at school. Oral DDAVP and oxybutinin, the anticholinergics for neurogenic bladder, were added, but he did not show any significant improvement.

For the treatment of severe dysconfiguration of the upper urinary tract and bladder, several cases have been treated with temporal percutaneous cystostomy, or with drainage with a double J catheter[26]. On the follow up renal sonogram and IVP, our patient showed no significant interval changes of megabladder, hydronephrosis and VUR. He finally underwent percutaneous cystostomy with a urine collection bag, which relieved him from the urgency symptoms and improved his daily life. It seems that the surgical drainage of urine is one of the good adjuvant therapies for the severe NDI cases in the respect to psychological relief and allowing social activity. The long term effects of medical treatment for NDI are still not satisfactory and we need further therapeutic trials, dietary control and surgical intervention are required in refractory cases.

한글 요약

유전자 분석검사로 확진된 선천성 신성 요붕증 1례

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신성 요붕증은 항이뇨호르몬의 정상적 분비에도 불구하고, 신장의 집합관의 항이뇨호르몬에 대한 반응이 저하되어 요농축능에 이상이 초래되는 질환이다. 특히 선천성 신성 요붕증은 대게 반성 열성 유전 양식을 따르는 유전 질환으로 매우 드물어 소아에서는 간헐적 보고만 있어 왔다. 어린 소아에서는 증상이 비특이적일 수 있고, 임상적 진단도 쉽지 않은데, 최근에는 항이뇨호르몬 수용체 유전자의 돌연변이들이 확인되어 유전자 검사로 확진이 가능하게 되었다. 기존의 보고들은 선천성 신성 요붕증이 진단된 환아들에 대한 이뇨제나 비스테로이드성 항염증제 등을 포함한 치료가 이루어진 증례보고이었으나 이들의 치료 후 장기적 추적 결과 보고가 극히 드물며, 이들 약제에 의한 치료 효과는 낮은 것으로 알려져 있다. 저자들은 극심한 이뇨로 인한 이차적 요로기관의 변형이 초래되었던 8세 소아에서 환아와 엄마의 말초 혈액 유전자 분석 검사상 Xq28 염색체 부위의 AVPR2 유전자의 돌연변이가 확인되었고 hydrochlorothiazide, indomethacin 및 amiloride 병합 치료 후 배뇨량은 하루 12리터에서 4리터로 감소하였고, 성장 발육도 정상이었으나 더 이상의 호전이 없고 일상 생활에 불편함이 지속되어 보조적 방광루 형성술을 시행받은 후, 증상 호전 및 심리적 안정을 얻었던 심한 선천성 신성 요붕증 1례의 5년간의 추적 관찰 결과를 보고하는 바이다.

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