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# Response to low dose indomethacin in two children with nephrogenic diabetes insipidus

## Odpowiedź na leczenie małą dawką indometacyny u dzieci z moczówką nerkową

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**Abstract**
Two children with nephrogenic diabetes insipidus (NDI) were treated with oral indomethacin (0.75-1.2 mg/kg/day) three times a day for a mean duration of 3 yrs. Remission occurred in both patients in terms of achieving a normal fluid balance and body growth and the drug was withdrawn in one patient after 2 yrs. The treatment was well tolerated and no side effects were noted. The mean duration of follow-up was 6.5 yrs. These long-term observations of a favourable response to low dose indomethacin in 2 children with NDI need to be tested on larger number of patients.
**Key words**
nephrogenic diabetes insipidus, cyclooxygenase inhibitors, indomethacin, children

**Streszczenie**
Prezentujemy 2dzieci z nerkowa moczówka prostą (NDI), które były leczone podana doustnie indometacyną((0.75-1.2 mg/kg/dzień) 3 krotnie w ciągu dnia średnio 3 lata. Remisja wystąpiła u obydwu pacjentów, osiągnięto prawidłową równowagę płynową i prawidłowe wzrastanie i lek u jednego pacjenta wycofano po 2 latach. Leczenie było dobrze tolerowane , nie obserwowano objawów ubocznych. Okres obserwacji wynosił średnio 6,5 roku. Taki okres obserwacji dobrej odpowiedzi na małą dawkę indometacyny u 2 dzieci z NDI wskazuje na konieczność przeprowadzenia obserwacji na większej liczbie pacjentów.
**Słowa kluczowe**
Nerkowa moczówka prosta, inhibitory cyklooksygenazy, indometacyna, dzieci

## Introduction

Nephrogenic diabetes insipidus (NDI) is a rare disease in children, characterized by the failure of renal tubules to respond to arginine vasopressin (AVP) due to a receptor or post receptor defect [1]. The resultant polyuria and polydipsia lead to a variety of non-specific symptoms like disturbed sleep and fatigability, anorexia, irritability, failure to thrive and developmental delay [1]. Severe symptoms like hypernatremic seizures, hyperosmolar dehydration and hypovolemic shock may occasionally cause death especially in infants and toddlers [1].

The aim of treating NDI is to reduce polyuria in order to avoid dehydration and hypernatremia, and therefore prevent early and late onset complications. The management is challenging and involves the use of hydrochlorothiazide alone or in combination with amiloride, indomethacin, rofecoxib or sometimes desmopressin [1, 2]. The combination therapy is usually associated with significant drug-related side effects and needs frequent



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monitoring [3]. The experience with long-term use of cyclooxygenase inhibitors as single agent therapy is limited. Frequently observed gastrointestinal, renal and haematopoetic complications with usual doses of indomethacin [4] as well as lower efficacy as compared to combination therapy [4, 5] including reports of failed response [2, 6] limit its use as a single drug for NDI. In this communication, we present our observations on prolonged use of low dose indomethacin for treatment of NDI in 2 children.

## Case report

***Case 1***

A 2 yr old boy presented with history of failure to thrive, delayed motor milestones, refusal to feed, increased urination and thirst for the past 1 yr. There was no history to suggest any chronic systemic illness or use of medications prior to the onset of symptoms. He was born at term after an uneventful pregnancy and weighed 2.5 kgs at birth. There was 2nd degree consanguinity between his parents. There was no family history of similar illnesses. The child had received a trial of low sodium diet and hydrochlorothiazide for 3 months and had also been receiving additional desmopressin nasal spray for about a month prior to referral to our centre. On examination, his weight was 9.6 kg (-2.07 SDS on WHO growth charts 2006), height 84.0 cm (-1.25 SDS) and head circumference 47.0 cm (-1.0 SDS). Systemic examination was unremarkable. Plasma urea and creatinine were 26.4 mg/dL (normal 5-18 mg/dL) and 0.8 mg/dL (normal 0.3-0.7 mg/dL) respectively on day 1, and 16 mg/dL and 0.6 mg/dL respectively on day 3 of hospitalisation. Serum potassium was 4.2 mEq/L (normal 3.5-5.0 mEq/L), calcium 9.2 mg/dL (normal 8.8-10.8 mg/dL, phosphorus 4.6 mg/dL (normal 3.8-6.5 mg/dL) and alkaline phosphatase (ALP) 276 U/L (normal 145- 420 U/L). Cranial magnetic resonance imaging (MRI) did not reveal any structural abnormalities in the hypophysis, hypothalamus and surrounding area, or calcifications. Other relevant laboratory parameters are shown in Table I.

***Case 2***

This 7.5 yrs old boy was symptomatic since infancy with polydipsia and polyuria, poor feeding, delayed milestones and growth retardation. Born to non-consanguineous parents at term, his birth weight was 2.8 kg. There was no history suggestive of any systemic disease or use of medications. He had been investigated elsewhere for diabetes insipidus and had shown minimal response to desmopressin therapy initiated 2 yrs back. General physical examination was unremarkable except for thin body built. His weight was 18.5 kg (-1.95 SDS) and height 115.0 cm (-1.69 SDS). Absence of posterior pituitary bright signal was noted in one of the 2 cranial MRI scans done elsewhere. No intracerebral calcifications were seen. Laboratory investigations revealed serum calcium 9.0 mg/dL (normal 8.8-10.8 mg/dL), phosphorus 4.2 mg/dL (normal 3.7-5.6 mg/dL), ALP 122 U/L (normal 145-420 U/L), potassium 4.0 mEq/L (normal 3.5-5.0 mEq/L), urea 16 mg/dL (normal 5-18 mg/dL) and creatinine 0.4 mg/dL (normal 0.3-0.7 mg/dL). Rest of the laboratory tests are shown in Table 1. An ultrasound examination of urinary system to look for effects of persistent polyuria was normal in both patients.

Both patients were started on oral indomethacin in a dose of 0.75 mg/kg/day given three times a day in addition to a diet with low sodium, normal protein and high calories. Parents were instructed to take care that the children received a generous fluid supply. At each follow up visit (3 per month for 1 yr and 6 per month subsequently), their weight, height, electrolytes, renal and liver functions, urine osmolality and 24 hour fluid balance was checked. Patient 1 showed a dramatic response in terms of remission of symptoms and marked catch up growth necessitating an increase in total indomethacin dose after 6 months of therapy (Table II). Absence of symptoms on drug-free days (2-3 days, usually over weekends, 1-2 times per month) during 2nd year of treatment prompted us to stop indomethacin in this patient. No recurrence of symptoms has occurred over subsequent 7 years of follow up. Patient 2 also showed a reduction in fluid intake and urine output but has continued to be symptomatic during drug-free days. The dose of indomethacin was increased to 1.2 mg/kg/day after 1 yr of therapy in patient 2. Both patients have shown consistent improvements in weight and height SDS over a mean duration of follow up of 6.5 yrs (Table II). The mean serum concentrations of repeated measurements of electrolytes, renal and liver functions and urine osmolality values at the follow up visits were all

**Table I.** Clinical and laboratory parameters at diagnosis and in follow up, results of water deprivation and desmopressin challenge, and duration of treatment

***Tabela I.*** *Kliniczne i laboratoryjne parametry w momencie rozpoznania i dalszym leczeniu, ocena zaburzeń wodnych i zmiany dawek desmopresyny w czasie leczenia*

| Patient no. | Pre-therapy urine volume (ml/kg/hr) | Serum sodium (mmol/L) | Basal urine osmolality (mOsm/kg) | Post water deprivation urine osmolality (mOsm/kg) | Post dDAVP osmolality (mOsm/kg) | Plasma AVP (pg/mL) | Mean urine volume in follow up (ml/kg/hr) | Mean urine osmolality in follow up (mOsm/kg) | Duration of indomethacin therapy (yrs) | Duration of follow up (yrs) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. | 8.4 | 146 | 86 | 163 | 176 | 6.0* | 2.2 | 466 | 2 | 9 |
| 2. | 6.2 | 154 | 112 | 158 | 202 | 19.5* | 2.6 | 516 | 4 | 4 |

Abbreviations: dDAVP, 1-desamino-8-D-arginine vasopressin; AVP, arginine vasopressin.
*normal range, 1-14 pg/mL

**Table II.** Auxological parameters in follow up
***Tabela II.*** *Parametry auksologiczne w trakcie obserwacji*

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Case 1** | Age (yr) | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 11 |
| | Weight (Kg)<br>SDS | 9.6<br>-2.07 | 13.2<br>-0.69 | 16.2<br>-0.07 | 17.8<br>-0.20 | 18.4<br>-1.08 | 19.2<br>-1.44 | 20.6<br>-1.55 | 23.0<br>-1.37 | 29.4<br>-1.06 |
| | Height (cm)<br>SDS | 84.0<br>-1.25 | 94.0<br>-0.75 | 104.4<br>0.26 | 112.8<br>0.63 | 121.5<br>0.95 | 126.0<br>0.81 | 131.0<br>0.74 | 135.0<br>0.51 | 143.5<br>0.02 |
| **Case 2** | Age (yr) | 7.5 | 8 | 8.5 | 9 | 9.5 | 10 | 10.5 | 11 | 11.5 |
| | Weight (Kg)<br>SDS | 18.5<br>-1.95 | 22.2<br>-0.98 | 23.2<br>-0.98 | 23.8<br>-1.11 | 24.6<br>-1.17 | 29.8<br>-0.35 | 31.4<br>-0.37 | 32.0<br>-0.59 | 33.2<br>-0.71 |
| | Height (cm)<br>SDS | 115.0<br>-1.69 | 120.0<br>-1.24 | 124.0<br>-0.97 | 126.2<br>-1.04 | 128.0<br>-1.16 | 135.5<br>-0.36 | 137.0<br>-0.56 | 140.0<br>-0.52 | 144.2<br>-0.33 |

within the specified normal ranges. There were no admissions required for severe dehydration or electrolyte disturbances. No therapy related adverse effects were reported by the parents.

## Discussion

The diagnosis of NDI, most likely congenital, in our patients was based on onset of suggestive symptoms during infancy, exclusion of central DI by normal/elevated AVP concentrations and normal MRI scans, and no response to dDAVP challenge during water deprivation test. However, we could not perform mutation analysis of AVP type 2 receptor (AVPR2) or water channel aquaporin 2 (AQP2) gene due to non-availability at our hospital and parents' financial constraints. The absence of bright spot in one of the MRI scans in patient 2 was probably a result of a component of secondary central DI due to long-untreated NDI or a normal physiological variation [7].

Although many potential therapeutic strategies which are currently under evaluation may become available in the future for effective antidiuresis in patients with NDI, the conventional treatment with a combination of diuretics with or without NSAIDs does not achieve sufficient control of polyuria [9]. Previous reports have suggested an increase in urine osmolality and decrease in urine volume by 30-70% in patients on diuretic therapy [2-6, 8, 9]. Only partial remission of polyuria has been documented in some of the largest series of patients on combination therapy [3, 5, 8]. An excellent response to combination therapy, however, has been documented in 2 infants [2, 6]. Lack of response to single drug therapy, particularly with indomethacin, has also been noted in previous reports [2, 6, 10]. There is only a single report demonstrating a good response to indomethacin as compared to ibuprofen as single agent [11]. In this context, the dramatic response that occurred in one of our patients and a sustained remission on therapy in the other patient is noteworthy. We believe that the first patient has probably achieved cure as he has remained asymptomatic after 7 yrs of withdrawing indomethacin. Both our patients also showed good catch up of physical growth. Such recovery of initial weight loss has been noted in earlier studies after initiation of the effective therapy [8, 9]. Some weight gain may also rarely occur as a side effect of indomethacin therapy. . The decision to start therapy with a single agent in first patient was taken on a trial basis, keeping in mind that provision of generous amount of fluids along with a low salt diet is sufficient to prevent disease consequences in many patients [3, 8, 9]. Also, this patient had shown a poor response to prior thiazide diuretic therapy. The observations on first patient encouraged us to opt for indomethacin in the second patient. We chose a small dose of indomethacin, as the side effects, particularly gastrointestinal, may be intolerable in children and prevent its long term use [4]. The inhibitory effect of indomethacin on urine volume in our patients was probably mediated by an AVP-independent water reabsorption resulting from an increase in solute reabsorption and consequent medullary hypertonicity. Water load studies conducted during 1980s have shown that indomethacin decreases the delivery of solute from the proximal tubule, reduces the fractional free water clearance, and increases the urine-plasma osmolar ratio and effectively reduces diuresis [12].

In conclusion, our observations suggest a good response to low dose indomethacin in 2 children with NDI. Further studies on larger number of patients with NDI are needed to validate these observations.

 

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