Internal Medicine and Medical Investigation Journal
E-ISSN: 2474-7750
Homepage: www.imminv.com

SYSTEMATIC REVIEW

Nephrogenic Diabetes Insipidus Due to Urinary Tract Obstruction: A Systematic Review

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ARTICLE INFO

Article history
Received: Aug 17, 2017
Accepted: Aug 28, 2017
Published: Oct 05, 2017
Volume: 2
Issue: 4

Conflicts of interest: None
Funding: None

Key words
Nephrogenic Diabetes Insipidus,
Obstructive Uropathy,
Urologic Diseases,
Diuresis

ABSTRACT

Background: Nephrogenic diabetes insipidus (NDI) due to obstructive uropathy is not widely known by physicians and hence not well represented in the literature. To better understand its presentation, clinical course, and available treatments, we conducted a systematic review of case reports on NDI due to urinary tract obstruction. **Material and Methods:** This observational study was a systematic review of 19 human cases found in the literature. It was done retrospectively to focus on whether NDI can occur due to obstruction of the urinary tract and, if so, what the mechanism (pathophysiology) is. **Results:** We found that the most common symptom of NDI due to urinary tract obstruction was polyuria. The most common cause of NDI due to urinary tract obstruction was cancer. The most common site for obstruction was the ureter. And the most common test used to confirm the diagnosis was failure to concentrate urine after the administration of desmopressin. Surgical intervention was the most common treatment to relieve obstruction. **Conclusion:** We found that urinary tract obstruction can cause NDI. With early diagnosis and timely relief of the obstruction, NDI can be reversible.

INTRODUCTION

Nephrogenic diabetes insipidus (NDI) is characterized by an inability to concentrate urine despite normal or elevated plasma concentrations of the antidiuretic hormone (ADH) [1]. It is a rare disease with an estimated incidence of three cases per 100,000 (0.003%), with a slightly higher incidence among men (60%) and prevalence of 1:25,000 [2] in the general population of the United States. NDI can be genetic or acquired. Many secondary causes of NDI have been described; urinary tract obstruction is one of the rarer and potentially reversible causes. However, it remains an understudied research area, and only a few cases have been described in literature.

Obstruction in the urinary tract as a cause of polyuria has been previously discussed in the literature. In the 1950s, Roussak et al [3] and Earley et al [4] coined the term "water-losing nephritis." Earley et al. concluded that the derangement in renal function parameters such as acidosis and the transient increase in blood urea nitrogen (BUN) occurred before the actual presentation of polyuria; hence, they preferred using the term water-losing nephritis, which simulates NDI. However, mild NDI is prevalent in the setting of re-

Published by Mehrabani Publishing LLC.

http://dx.doi.org/10.24200/imminv.v2i4.110

nal failure. Whether NDI stood out as a separate problem or as a direct consequence of urinary tract obstruction and not because of renal failure in such cases—especially in the context of the term "water-losing nephritis"—was a critical question. The same question was raised again in the cases presented by Landsberg et al. [5] in the *New England Journal of Medicine*, where the picture of renal failure confused the presentation of NDI as a separate entity in the event of obstruction of the urinary tract.

Due to the ambiguity on the subject, urinary tract obstruction as a cause of NDI is not widely known by physicians and hence not well represented in the literature. To better understand its presentation, clinical course, and available treatments, we conducted a systematic review of case reports on NDI due to urinary tract obstruction. Additionally, we offer recommendations on how this disease may be diagnosed early and what effective treatments may be provided to patients.

MATERIAL AND METHODS

To address this study's aim, we conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009) [38]. The PRISMA flow chart is detailed in Figure 1 (adapted from Liberati et al.).

Search Strategy

A systematic literature search was undertaken using PubMed, Medline, and the Cochrane Database of Systematic Reviews. Systematic search strategies were adhered to using the following search string:

((“diabetes insipidus, nephrogenic”[mesh terms] or (“diabetes”[all fields] and “insipidus”[all fields]

And “nephrogenic”[all fields]) or “nephrogenic diabetes insipidus”[all fields] or (“nephrogenic”[all fields] and “diabetes”[all fields] and “insipidus”[all fields])) and english[lang]) and ((“urologic diseases”[mesh terms] or (“urologic”[all fields] and “diseases”[all fields]) or “urologic diseases”[all fields] or (“obstructive”[all fields] and “uropathy”[all fields]) or “obstructive uropathy”[all fields]) and english[lang]) and english[lang]

In addition, citations and references within the identified articles were searched for further studies relevant to the review. We corresponded with experts in the field to ensure that all relevant studies were included in the review.

Study Selection

A study identified in the systematic searches was included in the review if it reported NDI caused by renal obstruction. We excluded other possible etiologies such as electrolytes or drugs that could cause NDI. We also excluded cases in which NDI itself caused hydronephrosis or ureteral dilation without any obvious urinary tract obstruction.

To ensure that all available studies were identified, the year of publication was not restricted and data were extracted until April 2017, but the search was limited to articles written in English.

Data extraction

To avoid selection bias, inclusion and exclusion criteria were agreed to and formalized before data extraction and analysis occurred. All articles identified from the initial searches were reviewed, and duplicates were removed. The titles and abstracts of the articles were screened for inclusion by all authors, with the remaining articles reviewed in full text and the exclusion criteria applied. In cases of disparities between the authors' judgments regarding suitability, they consulted to achieve agreement.

Study design

This observational study was a systematic review of 19 human cases found in the literature. It was done retrospectively to focus on whether NDI can occur due to obstruction of the urinary tract and, if so, what the mechanism (pathophysiology) is. To answer our first and main question, we studied the literature on human cases and selected 19 cases (Figure 1 and Appendix A). Table 1 was designed to address the mechanism (pathophysiology) behind our second question: if NDI did occur by urinary tract obstruction, what is the mechanism behind this phenomenon?

RESULTS

Search Process

We reviewed 19 cases of NDI (Appendix A) due to obstruction in the urinary tract in humans who presented with polyuria, polydipsia, or frequent urination (14 had polyuria). Cases that had post-obstructive diuresis were excluded (Figure 1).

In four cases, urinary output was 3-4.5 l/d; in one case, it was 10-15 l/d; in one case, it was 8 l/d; and in three cases, it was 2-2.5 l/d. Other case reports did not mention a definitive number for polyuria. Most patients were men (n=17); two were women. We noticed a substantial variation in age range, from 2 months to 85 years. The mean age was 36.05 years; the median age was 32; standard deviation was 28.62; and the standard error of mean was 6.56.

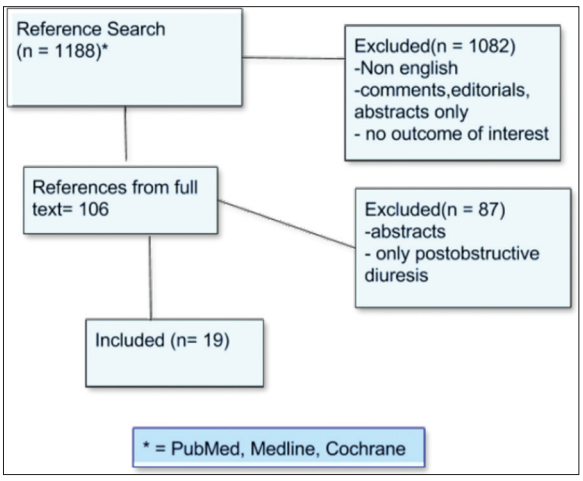

Figure 1. PRISMA flow chart showing the search and selection process that yielded the 19 selected articles

Table 1. Understanding the pathogenesis behind NDI due to urinary tract obstruction

Number	Author, year	Country	Design	Subject	UUO/BUO	Acute/Chronic	Comparator	Mechanism proposed	Result
1	Kim et al., 2001	Korea	Experimental study	Rats	BUO	Acute (48 hours)	Compared with rats without obstruction (without ligature)	Diminished expression of AQP with BUO	AQP1-3 decreased in cortex, outer and inner medulla whereas AQP 4 decreased in inner medulla. Immunoreactivities for AQP1 to AQP4 were also decreased in the obstructed kidneys.
2	Chunling li et al., 2003	USA	Experimental study	Rats	UUO	Acute (24 hours)	Sham-operated rats with low level of circulating vasopressin. Vasopressin-deficient brattleboro (BB) rats	Downregulation of AQP in response to UUO.	UUO: downregulation of AQP2, P-AQP, AQP3 and AQP4 in obstructed kidney -P-AQP2, AQP3, AQP4 in non-obstructive kidney was unchanged. -AQP1 was downregulated in both kidneys. Urinary concentration was decreased in obstructed kidney. AQP response in BB rats with low level of circulating vasopressin. Obstructed kidney: AQP2, P-AQP2, AQP3 decreased. Both kidneys: AQP 1 decreased.
3	Frokiaer et al., 1997	Denmark	Experimental study	Rats	UUO	Acute (24 hours)	Sham rats were used as comparator	Downregulation of aquaporin-2	Downregulation of aquaporin-2 mainly in the apical domain of the collecting duct principal cells in obstructed kidney. AQP-2 m-rna levels were downregulated in obstructed kidney.

(*Contd...*)

Table 1. (*Continued*)

Number	Author, year	Country	Design	Subject	UUO/BUO	Acute/Chronic	Comparator	Mechanism proposed	Result
									Free water clearance was greatly elevated in the obstructed kidneys and only moderately elevated in non-obstructed kidneys compared with sham-operated controls
4	Frokiaer et al.,1996	Denmark	Experimental study	Rats	BUO	Acute BUO was released 24 hours, 48 hours, and 7 days or not released.	Sham-operated rats	Downregulation of AQP-2 water channel in BUO	24 hours BUO: downregulation of AQP-2 expression in inner medulla; immediate onset of a predominant osmotic-dependent polyuria. 48 hours BUO: the reduction in AQP-2 expression persisted. Concurrent with a marked non-osmotic post-obstructive polyuria; reduced levels of AQP-2 in collecting duct principal cells. 7 days after release, the renal excretion of water and electrolytes had almost normalized, but AQP-2 downregulation was not partly reversed; urinary concentering capacity was reduced.

(*Contd...*)

Table 1. (*Continued*)

Number	Author, year	Country	Design	Subject	UUO/BUO	Acute/Chronic	Comparator	Mechanism proposed	Result
5	Topcu SO et al.,2011	Denmark	Experimental study	Neonatal rats	PUO with solitary kidney	48 hours to 14 days	Sham-operated rats	To determine the hemodynamic and molecular changes in the solitary kidney in response to partial ureteral obstruction (PUO)	A. AQP 1 was markedly decreased. B. Decreased urinary sodium excretion and a significant reduction in urinary osmolality from the obstructed kidney.
6	Murer et al.	Italy	Observational study	Humans (12 children)	12 children with UUO due to pyeloure-teral junction disease	Observed urine from day 1 to day 5 after pyelopla-sty	Contralateral non obstructed kidney	Decrease in AQP-2 and increase in PGE-2 is associated with post-obstructive polyuria in post-obstructive kidney	All results are compared to the contralateral kidney -:AQP2 decreased 24 hours later (54%) and 5 days later (22%) -urinary output: high all 5 days -sodium: high on days 1 and 4 -urinary clearance all 5 days -crcl no change for 4 days On day 5: lower than the contralateral kidney -PGE2 2x higher than contralateral on day 1
7	Divas Aimia AJ et al., 1998	USA	Experimental study	Rats	-	-	-	Role of aquaporin in vasopressin activated water reabsorption in the kidney collecting duct.	A. AQP1 is involved in water reabsorption in the kidneys, proximal tubules, and the thin descending loop of henle. B. AQP2 is the only water channel that is activated by vasopressin for enhancing water absorption in the kidney collecting duct.

(*Contd...*)

Table 1. (*Continued*)

Number	Author, year	Country	Design	Subject	UUO/BUO	Acute/Chronic	Comparator	Mechanism proposed	Result
8	Tamma G et al.,2003		Experimental study	Rats	-	-	-	The prostaglandin E 2 analogue sulprostone antagonizes vasopressin-induced antidiuresis through activation of rho.	A. Stimulation of EP3 receptors inhibits ANP-induced AQP2 translocation in imcd cell. B. Stimulation of EP3 receptors induces the formation of stress fibers in IMCD cells. C. Bidirectional control of rho by antidiuretic and diuretic agents in IMCD cells. D. EP3 receptor stimulation Prevents AQP2 translocation independently of camp. E. EP3 receptor stimulation neither induces formation of Inositol trisphosphate nor elevation of cytosolic ca2+in IMCD cells.
9	FA Gulmi et al.,1995	USA	Experimental study	Dogs	UUO, BUO, and BUO with saline volume repletion	Acute (48 hours)	3 groups of dogs compared with each other	Volume expansion enhances the recovery of renal function and prolongs the diuresis and natriuresis after release of BUO mediated by ANP	A. ANP level is increased in BUO. B. No increase in urine output and sodium excretion in UUO (group 1). C. Initial increase in urine output and sodium excretion (group 2 and 3). D. Volume expansion during BUO enhances post-obstructive diuresis and natriuresis and allows a greater recovery of GFR after release of the obstruction.

(*Contd...*)

Table 1. (*Continued*)

Number	Author, year	Country	Design	Subject	UUO/BUO	Acute/Chronic	Comparator	Mechanism proposed	Result
10	Ryndin I et al.,2005	USA	Experimental study	Rats	BUO	Acute (24 hours)	A. Renal function by clearance method in sham-operated and BUO rats B. Renal response to ANP in abovementioned rats with or without pretreatment with phosphoram-idon (NEP inhibitor)	ANP contributes to post obstructive diuresis after release of BUO	A. Response to ANP and renal NEP receptor activity were preserved 24 hour BUO. B. NEP augmented to ANP in increasing GFR, natriuresis, and diuresis. C. After release of 24-hour BUO, intense vasoconstriction persists, but it is associated with natriuresis and diuresis despite decrease in GFR. D. ANP administration increases GFR, natriuresis, and diuresis. E. Degradation of ANP in proximal tubule accentuates these renal responses. F. ANP is involved in post-obstructive diuresis and natriuresis as well as accentuating renal vasoconstriction in BUO.
11	ML Purkerson et al., 1989	USA	Experimental study	Rats	BUO, UUO	-	A. BUO was examined by the intravenous infusion of heparin with or without the exogenous administration of atrial peptide B. Control rats or rats with UUO.	Role of ANP in the natriuresis and diuresis that follows relief of obstruction	A. Heparin administration markedly blunted the natriuresis and diuresis observed after exogenous administration of atrial peptide following release of BUO.

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Table 1. (*Continued*)

Number	Author, year	Country	Design	Subject	UUO/BUO	Acute/Chronic	Comparator	Mechanism proposed	Result
									B. Heparin administration did not decrease the natriuresis and diuresis seen in the experimental kidney after relief of UUO.
12.	Fried TA et al.,1998	USA	Experimental study	Rat	-	-	Delivery of chloride to the superficial late distal tubule and the base and tip of the papillary collecting duct in synthetic analogue of atrial natriuretic peptide (ANP) or vehicle alone	Tubular site of action	ANP inhibits reabsorption in some tubular segments between the superficial late distal tubule and papillary collecting duct base as well as in the accessible portion of the papillary collecting duct.
13	Baum et al.	USA	Observational study	-	-	-	-	Post-obstructive diuresis	Massive diuresis after obstruction is divided into three categories: A. salt diuresis; B. urea diuresis; and C. water diuresis.
14	Sonnen-berg. H et al.	Canada	Experimental study	Rats	BUO	Acute (24 hours)	Sham-operated rats	The role of the medullary collecting ducts in post-obstructive diuresis.	(A) The medullary collecting duct is the critical nephron segment affected by ureteral obstruction, since post- obstructive diuresis occurred despite reduced delivery of fluid from the more proximal nephron; (B) the net addition of sodium to the medullary collecting duct observed during post-obstructive

(*Contd...*)

Table 1. (*Continued*)

Number	Author, year	Country	Design	Subject	UUO/BUO	Acute/Chronic	Comparator	Mechanism proposed	Result
									diuresis is probably a direct effect of obstruction, since it was found during post-obstructive diuresis after relief of bilateral or unilateral ureteral ligation, but not with urine reinfusion alone; and (C) blood-borne factors are important in the development of post-obstructive natriuresis and diuresis, and probably act by increasing the fraction of filtered sodium and water delivered from the proximal and distal tubule to the collecting duct.
15	Harris RH et al.,1975	USA	Experimental study	Rats	BUO, UUO with contralate-ral nephrecto-my (UUO-NX) and UUO with continuous intravenous reinfusion of urine from the intact contralateral kidney (UUO-reinfusion)	Acute 24 hours	UUO rats and sham-operated rats	To investigate the pathogenesis of post-obstructive diuresis	A. Uretic factors that are normally excreted in the urine, and which, when retained (as in BUO or UUO-NX rats) or returned to the circulation (as in UUO-reinfusion rats) exert a diuretic effect. B. UUO rats infused with urea exhibited post-obstructive diuresis, if extracellular volume contraction was prevented. C. Intact kidney of UUO-reinfused rats displayed a massive unilateral diuresis and natriuresis, further suggesting the presence of potent diuretic factors in the urine.

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Table 1. (*Continued*)

Number	Author, year	Country	Design	Subject	UUO/BUO	Acute/Chronic	Comparator	Mechanism proposed	Result
16	Douglas r Wilson, 1972	Canada	Experimental study	Rats	Unilateral partial ureteral obstruction for several weeks	Chronic	1) Group a, control sham-operated rats, 10 animals; 2) Group b, chronic obstructive nephropathy with the catheter below the level of the ureteral obstruction, nine animals; and 3) Group c, chronic obstructive nephropathy with the catheter placed above the level of the ureteral obstruction, the post-obstructive group, eight animals.	To study the effect of chronic ureteral obstruction on individual surface nephron function and whole kidney clearance in the absence of volume expansion or solute loading, using micro-puncture techniques.	A. Proximal intratubular pressure was slightly increased when compared to sham-operated control animals B. Tubular fluid flow rate was reduced by 35%, fractional reabsorption was increased by 8%, and single nephron filtration rate was 76% of control values C. Disproportionately high surface nephron to whole kidney glomerular filtration rate (GFR) was present D. Increased fractional excretion of sodium and diminished urine osmolality observed from decreased reabsorption in the distal nephron and/or impaired function of the deep nephrons and renal medulla.
17	Kishimo-to I et al.	USA	Experimental study	Rats	-	-	1.wild-type mice 2.GC-A- deficient mice	The heart communicates with the kidney exclusively through the guanylyl cyclase-a receptor and results in natriuresis and diuresis mediated by ANP	A. Infusion of ANP results in substantial natriuresis and diuresis in wild-type mice but fails to cause significant changes in sodium excretion or urine output in GC-A-deficient mice.

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Number	Author, year	Country	Design	Subject	UUO/BUO	Acute/Chronic	Comparator	Mechanism proposed	Result
									B. ANP concentrations were markedly elevated in both wild-type and GC-A-null mice. C. After volume expansion, urine output as well as urinary sodium and cyclic GMP excretion increased rapidly and markedly in wild-type mice, but the rapid increases were abolished in GC-A-deficient animals.

ANP; atrial natriuretic peptide, AQP; Aquaporin (family of membrane channel proteins); BUO; Bilateral Ureteral Obstruction; CrCl; creatinine clearance, EP3; Prostaglandin EP3 receptor; GFR; glomerular filtration rate; GC-A; Guanylate cyclase-A;
GMP; Guanosine 5'-Monophosphate, IMCD; Inner Medullary Collecting Duct; NEP; Natriuretic peptide; UUO; Unilateral Ureter Obstruction
PUO; Partial Ureteral Obstruction, PG E 2; Prostaglandin E2.

Six cases of obstruction were due to cancer: ovarian cancer (n=1), cancer of the ureter (n=1), leiomyosarcoma (n=1), prostate cancer (n=2), and metastatic rectal cancer (n=1). In the other thirteen cases, three were due to bladder neck obstruction, one was due to diverticulum, two were due to obstruction in the posterior urethral valve, one was due to benign prostate hyperplasia, three were due to fibrotic fascia covering the ureters, and two were due to ectopic ureterocele. In one case, the site of obstruction was not detected. The most common site of obstruction was the ureter (n=9), followed by the bladder (n=4), urethra (n=3), and both the bladder and ureters (n=2).

In twelve cases, imaging techniques were used to determine the cause of obstruction (computed tomography scan, n=2; endoscopy, n=2; intravenous pyelogram with cysto-urethrogram, n=2; cysto-urethrogram alone, n=5; and retrograde pyelography, n=1). In four patients, evidence of obstruction was found after surgery; in one patient, evidence of obstruction was found after prostate biopsy; and in one patient, who presented with benign prostate hyperplasia, obstruction was diagnosed by physical examination.

Of the nineteen cases, the water deprivation test was performed in seven patients to rule out the function of ADH. Whether the water deprivation test was administered was not mentioned in other cases. In thirteen cases, the desmopressin test was performed with either vasopressin or Pitressin to rule out central DI from nephrogenic DI; in all thirteen cases, the results indicated the nephrogenic cause of DI. In four cases, neither of the abovementioned tests were performed. Data from other cases regarding the desmopressin test were not reported. Only one case report reported the use of the diethylenetriaminepentacetate scan.

Sixteen patients underwent surgical treatment to relieve the obstruction; three patients did not undergo surgical treatment. Of the three patients who did not undergo surgical treatment, one who presented with recurrent rectal cancer had technical difficulties related to surgical treatment and also refused further admission to the hospital; one was a 15-year-old girl with a distended bladder for whom the cause of obstruction could not be detected; and one was not treated surgically, and no reason was provided as to why.

Of the sixteen patients who were treated surgically for obstruction, all experienced relief from NDI symptoms. Of the nine cases in which it was reported when urine output returned to normal or less than 2.7 l/day: in two cases, it took 48 hours post-operatively; in three cases, it took 7 days; in one case, it took 9 days; in one case, it took 1 month; in one case, it took 5 months; and in one case, it took 8 months. For seven cases, no timeline was mentioned. Overall improvement in complaints of NDI had a wide range: from 2 days to 8 months. Also, the patient who had metastatic rectal cancer and refused surgical treatment for urinary tract obstruction died after 2 months.

Of the sixteen patients who were treated surgically, fourteen experienced complete relief of symptoms after surgical treatment, while two patients experienced partial relief; of these two patients, the one reported by E. W. Ramsey et al [28] returned after 3 years of surgical treatment, the other was a 5 month old child who presented with a complex case requiring multiple surgical procedures, but eventually NDI symptoms were controlled with a low-salt diet [29].

Of the nineteen cases, we reviewed six cases that were treated with thiazides in addition to surgical treatment. This is a known treatment for NDI and causes paradoxical effects. In all six cases, thiazides were given post-operatively. Data as to how long this treatment was continued were not available, except in two cases. In one case, it was stopped 1 month after the surgery; in the other case, it was discontinued 1 year after surgery because of an attack of gout. The two patients who were prescribed thiazides experienced a decrease in urinary output from 4 l/d to 2 l/d. In one patient, an improvement from 2.5 l/day to 1.7 l/day was observed while using thiazide along with amiloride. In the other patient, urinary output decreased from 8 l/d to 5 l/d after the addition of thiazide, and there was further improvement in urinary output after the addition of diclofenac, from 5 l/day to 4 l/day. One of the patients who received thiazide may have experienced an improvement in urinary output, but this was not clearly stated. One case report described weight gain by a child patient after the administration of thiazide. We also noticed that in four patients, another drug besides thiazide was used as well: in one case, alpha glucosidase inhibitor was administered before removal of the obstruction, which did not improve polyuria symptoms; in one case, amiloride was administered; in one case, diclofenac sodium was used for 1 month prior to surgery and 1 month postoperatively, which helped improve symptoms of polyuria; and in one case, stilbestrol was administered postoperatively and may have played a role in the improvement of symptoms, but this was not clear.

Only two case reports mentioned the results of kidney biopsy, suggesting mild to chronic inflammation.

In our review, thirteen case reports provided data for BUN. Of these, six cases had normal BUN levels (7-20 mg/dl). Three cases had an increase in BUN levels (110 mg/dl, 39 mg/dl, and 80 mg/dl) due to dehydration; and after the infusion of fluids, BUN levels returned to normal in two cases (16 mg/dl and 13 mg/dl, respectively), and in the third case BUN decreased to 28 mg/dl preoperatively. In four cases, BUN ranged between 25 mg/dl and 37 mg/dl and returned to normal in three cases, although one case report did not mention any post-operative results.

Of the thirteen case reports that included creatinine values, six patients had normal values (0.6-1.3 mg/dl). In six cases, creatinine values ranged between 1.6 mg/dl and 7 mg/dl and returned to normal in three cases; in the other three cases, no post-operative data were available. Of these six cases, in one case report, although creatinine levels decreased from 3.2 mg/dl to 1.1 mg/dl 6 months postoperatively, the patient still experienced chronic renal failure. In one case, creatinine clearance was 22 and 49 post-operatively after vasopressin administration and the water deprivation test, respectively. In one case of a patient with rectal cancer who was not operated on for NDI, initially the patient presented with normal kidney function, but later his condition deteriorated and chronic renal failure occurred.

In four cases, plasma osmolality was within the normal range (275-310 mOsm/kg H_2O), and we observed hypos-

thenuria in these cases. In two cases, plasma osmolality was slightly raised (396 mOsm/kg H_2O) due to dehydration, but hyposthenuria was observed in these cases too. In six cases, urine osmolality increased compared to plasma osmolality (i.e., hypersthenuria) and was within the normal range of 300-900 mOsm/kg H_2O postoperatively. One patient with rectal cancer presented with hyposthenuria. He was not treated and died due to gastrointestinal bleeding; autopsy to further investigate the cause was declined. In one case, no data were available regarding preoperative values, but hypersthenuria was observed post-operatively with and without thiazides. In one case, urine osmolality was 403 mOsm/kg H_20 and 409 mOsm/kg H_20 without and with dehydration diet, respectively, but no data were available for plasma osmolality or postoperative changes. In nine cases, no data were available regarding plasma and urine osmolality. All 19 patients were treated in an inpatient healthcare facility, since they had to be treated surgically to remove the obstruction.

Pathogenesis

To better understand the mechanism behind NDI occurrence due to urinary tract obstruction, we selected an additional 17 cases (16 on animals and 1 on twelve children) (Table 1).

Relief of obstruction (bilateral ureteral obstruction [BUO] and unilateral ureteral obstruction [UUO]) may cause period of diuresis by several mechanisms. One of those mechanisms is due to water channels aquaporin (AQP); many studies in rats were done, showing that serious degradation and downregulation of aquaporin channels was the principal phenomenon. AQPs are intrinsic membrane proteins that act as water-selective channels. Of the 17 studies (Table 1) that we examined to better understand the pathogenesis of how NDI develops after urinary obstruction, eight studies (7 studies in animals and 1 study in humans) confirmed the downregulation of an AQP channel in a post-obstructed kidney. Several studies showed downregulation of AQP 1-4, mostly in the cortex, outer medulla, and inner medulla [6,7]. A similar phenomenon was observed in both BUO and UUO [8,9]. A study with partial ureteral obstruction also showed a decrease in AQP 1 [10].

One study examined 12 children who underwent pyeloplasty due to congenital unilateral hydro-nephrosis, as a result of pyeloureteral junction disease [11]. In this study, AQP 2 levels in post-obstructed kidneys were compared to non-obstructed kidneys for 5 days. The results were a decrease in AQP 2 channels in obstructed kidneys: 54% in 24 hours and 22% in 5 days.

This gives us a valid reason to deduce that whenever a kidney is exposed to an obstruction, downregulation of AQP occurs because of deeper changes at the cellular level. AQP 2 is the only water channel that is activated by vasopressin. Vasopressin-induced c-amp mediated pathway is responsible for phosphorylation and insertion of AQP 2 channels. In an obstruction, the c-amp pathway gets blunted and is responsible for downregulation of AQP 2 channels [12]. Moreover, in one study, while examining AQP 2, an increase in prostaglandins E-2 (PGE-2) was observed in the urine from the obstructed kidney. The authors hypothesized that increased PGE-2 (rho activation and subsequent formation of f-actin stress fibers) [12] may also be responsible for downregulation of AQP channels [11].

Many studies also examined another mechanism: atrial natriuretic peptide (ANP). Gulmi et al. performed an acute experiment on 18 dogs divided into three groups based on UUO and BUO with and without volume repletion with sodium chloride. In the UUO group, they observed no increase in diuresis and natriuresis; however, initial diuresis and natriuresis were observed in the BUO group of dogs. Natriuresis persisted in the group of dogs in which volume repletion was performed, and a significant rise in ANP was observed after 48 hours of BUO [13]. An acute study in rats by Ryndin et al. demonstrated a similar effect, where the release of BUO for 24 hours showed a persistently intense vasoconstriction, which reduced the glomerular filtration rate (GFR); however, this case was associated with natriuresis and diuresis [14]. The basic mechanism understood is that ANP is increased more in BUO than in UUO, which explains that the volume expansion due to an obstruction causes increased levels of circulating ANP [13,15], but the same is not observed in UUO. ANP-induced natriuresis is due to the increase in GFR, and ANP inhibits the transport of sodium to the medullary collecting duct. At the molecular level, this function is served by binding to the natriuretic peptide receptor-A (NPR-A) receptor, expressed in the kidneys and the vasculature [16]. NPR-C serves to remove ANP and acts as the clearance receptor. Additionally, ANP inhibits reabsorption of chloride in the tubular segments between the superficial late distal tubule and the papillary collecting duct, as well as in the accessible portion of the papillary collecting duct, thereby increasing natriuresis [17].

Other mechanisms may contribute to polyuria (Figure 2) in addition to AQP and ANP, such as accumulation of solutes and fluid retention due to obstruction, which could result in diuresis [18]; however, once the excess solutes are eliminated, normal renal function may return [19,20]. Furthermore, in clinical studies, decreased sodium channels in the proximal tubule, the thick ascending limb, the distal convoluted tubule, and the inner medullary collecting duct; collapse of the inner medullary osmotic gradient; and damage to the medullary collecting duct after release of chronic post-obstructed phase have been demonstrated. It has also been observed that, in chronic obstructions of the urinary tract, additional deeper nephrons are damaged and superficial nephrons are spared [21].

DISCUSSION

In the 19 cases that we reviewed, all patients had evidence of urinary obstruction and developed signs and symptoms consistent with NDI. The most common presenting symptom that prompted suspicion of NDI was polyuria. In most cases, polyuria was accompanied by polydipsia. Although the causes of obstruction varied, cancer was the most common cause. The most common site of obstruction was the ureter.

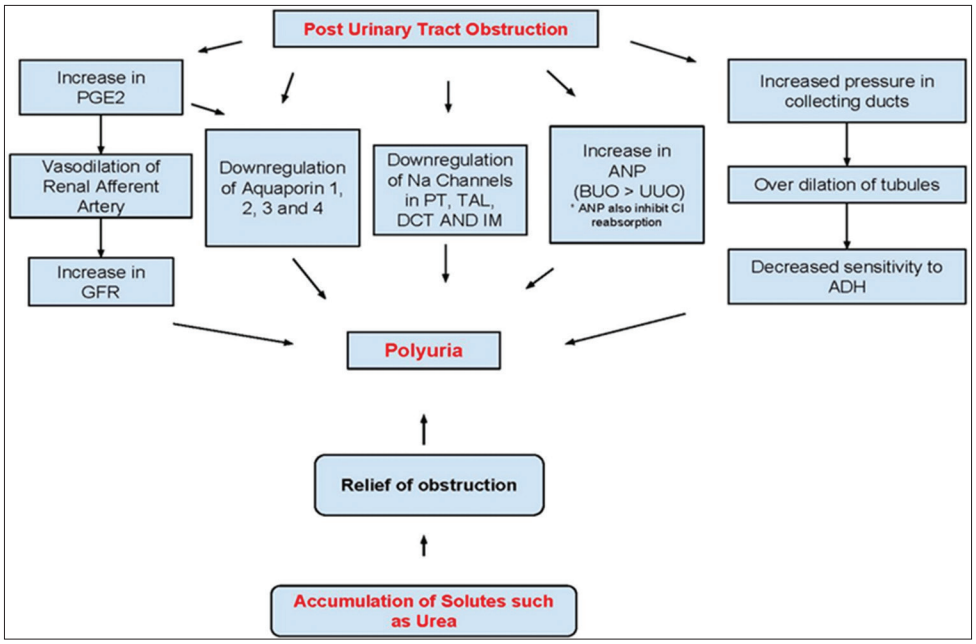

Figure 2: Mechanisms leading to polyuria.

In almost 20% of the cases, the obstruction was at the level of the bladder.

In 63% of the cases, the cause of obstruction was determined by radiologic investigations, including computed tomography scan, cysto-urethrogram, and retrograde pyelography. In 21% of the cases, the obstruction was confirmed surgically.

The clinical diagnosis of NDI relies on the demonstration of subnormal ability to concentrate the urine despite the presence of the antidiuretic hormone pituitary-derived arginine vasopressin. The measurement of serum sodium concentration and the failure to concentrate the urine normally in the presence of high plasma vasopressin concentration and after parenteral administration of vasopressin or desmopressin are diagnostic of NDI [22]. The water deprivation test helps distinguish between the different causes of polyuria. This test should be performed by experienced physicians and entails withholding any fluid intake from the patient. The normal physiologic response to the water deprivation test is an increase in the antidiuretic hormone as the plasma osmolality increases and, subsequently, an increase in urine osmolality [23,24].

In our study, 36.8% of patients underwent the water deprivation test; the most common test used to confirm the diagnosis of NDI was failure to concentrate urine after desmopressin administration.

Surgical interventions were the most common method of relieving the obstruction, accounting for 84% of the total case reports reviewed. In these studies, all patients responded with a decrease in urinary output and experienced better concentration of urine: 87.5% of patients had complete relief of symptoms and 12.5% had partial relief. In 31% of the cases, thiazides were used. In one case, thiazides caused a significant decrease in urinary output with the concomitant use of non-steroidal anti-inflammatory drugs.

CONCLUSION

We found out that urinary obstruction in its different forms can cause NDI and that with early diagnosis and timely relief of the obstruction, NDI can be reversible. Cancer was the most common cause of the obstruction. Imaging techniques were used to determine the site of obstruction; inability to concentrate urine and desmopressin tests were the most common methods of diagnosis; and surgical interventions were the most common treatments.

Limitations

Our study could be limited by publication bias. We understand that we studied only case reports of a rare and underreported condition in humans and that the reasons for obstruction, the treatment methods, and the clinical course can be different in clinical settings. Other biases would be the English-language bias and the database bias.

As far as the pathogenesis of NDI is concerned, all except one referenced study was an animal study. More studies in humans are needed to evaluate and better understand the mechanism behind urinary tract obstruction that causes NDI. Our data should be interpreted with these limitations in mind.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this study.

ACKNOWLEDGEMENTS

This has been a collaborative project from the start. We gratefully acknowledge the thoughtful comments, corrections, and advice of many medical students and faculty members who have supported us in the writing of this review.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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Appendix A (Result table)

Name of Paper	Author	Type of obsrtuction	Evidence of obstruction	Operative evidence	Did DI resolve after relief of obstruction?	Level of obstruction - kidney/ ureter/urethera	Pre- existing condition	How long it took patient to get better
1A case of nephroge-nic diabetes insipidus caused by partial bilateral ureteral obstructi-on due to advanced stage ovarian ca	Tayfun gungor et al [26]	Yes - ovarian tumor	Abdominal ct	Yes- debulking surgery-	Yes after the addition of hctz	Ureter	No	9 days
2Water-losing nephritis. A syndrome simulating diabetes insipidus - case 1	N. J. Roussak and s. Oleesky [3]	Yes- defect of renal tubular function occurring in myelomatosis	Ndi due to defect in renal tubular function due to myelomato-sis	Not done	Not Mentio-ned	Not Mentioned	Myeloma	Died
3Water-losing nephritis. A syndrome simulating diabetes insipidus - case 2	N. J. Roussak and s. Oleesky [3]	Yes- enlarged prostate gland- carcinoma prostate	Cystoscopy	Prostatect-omy	Yes	Ureter	Htn	3 months
4Nephrog-enic diabetes insipidus due to hydronep-hrosis in a patient with a solitary kidney	Katsunobu yoshioka et al [27]	Yes- cancer of the ureter	Retrograde pyelography	Yes-drainage using a nephrosto -my tube	Yes after one month	Ureter	Nephrec-tomy of right kidney due to TB	1 month
5Nephrog-enic diabetes insipidus associated with massive hydronep-hrosis and bladder neck obs	E. W. Ramsey et al [28]	Yes- bladder neck obstruction diverticulum on right side	Endoscopy	Diverticul-ectomy	Yes for a while - upto 3 years	Bladder neck obstruction+heridatary vasopressin insensitive DI	Htn n obesity	Na - 5 months
6Nephrog-enic diabetes insipidus associated with posterior urethral valves	Neil H.BaumM.D. et al [29]	Prostatic urethera- suprapubic mass-inframontane valves	Panendosco-py	Resection	Not complet-ely and returned after resection - but NDI well control-ed with low salt diet	Urethera	Not Mentioned	Not Menti-oned
7"Nephro-genic diabetes insipidus associated with bilateral ureteral obs."	Akhhiko kato et al [30]	Leiomyosarcoma	Yes post-surgical recurrence	Yes, nephrosto-my took 5 months from 8 to 2.5 l	Yes	Both ureter	Ileal leiomyo-sarcoma	6 months
8Nephrog-enic diabetes insipidus secondary to obstruct-tive uropathy – an unusual presentation- a case report	Habibur rehman et al [31]	Posterior urethral valve	Cystogram and urethrogram	Cystoscopy	Yes	Bladder/urethra	Posterior urethral valve	7 days

(*Contd...*)

Appendix A (Result table)

Name of Paper	Author	Type of obsrtuction	Evidence of obstruction	Operative evidence	Did DI resolve after relief of obstruction?	Level of obstruction - kidney/ ureter/urethera	Pre- existing condition	How long it took patient to get better
9Extreme polyuria in obstruct-tive uropathy A case of water losing nephritis in an infant.	Earley LE et al [4]	Bladder neck obstruction	Cystogram and urethrogram	Wedge resection	Yes	Urinary bladder	Cystos-copy	8 months
10Petre-ssin resistant diabetes insipidus with massive hydrone-phrosis	Emanuel silverstein and louis tobian [32]	Bladder neck obstruction	Retrograde urethrogram	Not Mentioned	Not Mentioned	Urinary bladder	4 previous hospital admissions , 2 for pneumonia, 1 for pyuria and dysuria, and 1 for pyelonep-hritis and broncho- pneumonis	Not Mentioned
11Neph-rogenic di and obstruct-tive uropathy	Jan Wiggelinkhuizen et al [33]	Present, right ectopic ureterocele also had mild bladder outlet obstruction	Yes, iv pyelogram and cysto-urethrogram	Yes, terminal ureterosto-mies and excision of ureterocele	DI resolved only when hctz was introduc-ed.	Ureter	Not Mentioned	6 weeks
12Neph-rogenic DI and obstruct-tive uropathy	Jan Wiggelinkhuizen et al [33]	None physically, but over distention of bladder caused urine backflow	No	Not Mentioned	No		Diagnosed as ndi at age 3	Not Menti-oned
13Peri-ureteral fibrosis, with a diabetes insipidus like syndrome occuring with progressive partial obstruct-tion of a ureter unila-terally	Dobald knowlan et al [34]	Yes, fibrotic fascia covering the ureter at l2 and l5 level which was post-surgical after tumor removal in the other kidney	Yes, exploratory operation	Yes, fibrosis removal from ureters	Yes	Ureter	Htn, non-function-ing left kidney	Within a week
14Peri-ureteral fibrosis, with a diabetes insipidus like syndrome occurring with progre-ssive partial obstruct-tion of a ureter unila-terally	Dobald knowlan et al [34]	Yes, left ureter completely covered in thick fibrotic fascia	Yes, exploratory operation	Yes, fibrosis removal from ureters	Yes	Ureter	AAA	1 month

(*Contd...*)

Appendix A (Result table)

Name of Paper	Author	Type of obsrtuction	Evidence of obstruction	Operative evidence	Did DI resolve after relief of obstruction?	Level of obstruction - kidney/ ureter/urethera	Pre- existing condition	How long it took patient to get better
15Peri-ureteral fibrosis, with a diabetes insipidus like syndrome occurring with progress-ive partial obstruct-tion of a ureter unila-terally	Dobald knowlan et al [34]	Yes, ureter covered under dense fibrotic tissue	Yes, explora-tory operation	Yes, fibrosis removal from ureters	Yes	Ureter	Pneumonia, hernia inguinal	More than a month
16A case of NDI caused by obstructive uro-pathy due to prostate cancer	Hong E.G et al [35]	Yes, prostate adenocarcinoma, ureteral obstruction	Yes, prostate biopsy with TRUS	Yes, TURP	Yes	Ureter	Htn	Discha-rged in 4 days
17Neph-rogenic diabetes insipidus. An unusual presentation of recurrent rectal cancer	Frank Nobels MD et al [36]	Yes, recurrences of metastatic rectal cancer invading post. Wall of bladder and distal portions of both ureter	Yes, CT scan and cystoscopy	No evidence	No, patient refused further treat-ment	Post wall of bladder and distal portions of both ureters.	Had rectal adeno-ca which was resected. After 8 months of surgery patient suddenly developed polyuria & it was when he was diagnosed with recurrence of rectal cancer with NDI.	Patient died after 2 months
18Nep-hrogenic diabetes insipidus and obstruct-tive uropathy	A.aaronson and j.wiggelinkhuizen [37]	Yes, in infancy an ectopic ureterocele associated with right duplex system had been unroofed and both right ureters brought to the surface as cutaneous end ureterostomies, because of that post. Wall of the unroofed ureterocele was clearly seen to bulge down during micturition (due to polyuria) and produce an obstructive lip at the bladder neck.	Yes, did not see by cystoscopy but was seen by video micturition cysto-urethro-graphy	Yes, surgery was done to remove the affected portion of the trigone and the right lower moiety of the ureter was re-implanted	Did not mentio-ned	At bladder neck	Patient had ectopic ureterocele with right duplex system	After surgery it got better. But did not men-tion exact days.
19Hyper-natremia compli-cating partial urinary tract obstruct-tion	Lewis landsberg, md et al [5]	Yes, BPH (mild) but main feature was marked phimosis	Yes, physical examination	Yes, surgery to relieve phimosis	Yes	Urethra	BPH and phimosis	2nd day after surgery

AAA; Abdominal aortic aneurysm, BPH; Benign prostatic hyperplasia, Ca; Carcinoma, CT; Computed Tomography, DI; Diabetes Insipidus, HTN; Hypertension, HCTZ; Hydrochlorothiazide, Obs; Obstruction, NDI; Nephrogenic diabetes insipidus, TB; Tuberculosis, TURP; Transurethral resection of the prostate, TRUS; Prostate ultrasound or trans-rectal ultrasound.