**Central diabetes insipidus and cisplatin induced renal salt wasting syndrome:
a challenging combination.**

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Text word count: 1295

Abstract word count: 97

Tables: 1

Figures: 1

Supplemental files: 1

Short running title: Diabetes insipidus and renal salt wasting

Keywords: diabetes insipidus, renal salt-wasting syndrome, syndrome of
inappropriate anti-diuretic hormone secretion, cerebral salt-wasting syndrome,
hyponatremia.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1002/pbc.25910](https://doi.org/10.1002/pbc.25910).

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21 Abbreviations:

ADH	anti-diuretic hormone
CSWS	cerebral salt-wasting syndrome
CNS	central nervous system
DI	diabetes insipidus
GFR	glomerular filtration rate
PNET	primitive neuroectodermal tumor
RSWS	renal salt-wasting syndrome
SIADH	syndrome of inadequate anti-diuretic hormone secretion
TBI	traumatic brain injury

Abstract

We describe a 2 year old female with a suprasellar primitive neuroectodermal tumor (PNET) and central diabetes insipidus (DI) who developed polyuria with natriuresis and subsequent hyponatremia 36 hours after cisplatin administration. The marked urinary losses of sodium in combination with a negative sodium balance led to the diagnosis of cisplatin induced RSWs. The subsequent clinical management very challenging. Four weeks later she was discharged from ICU without neurological sequela. The combination of cisplatin induced RSWs with DI can be confusing and needs careful clinical assessment as inaccurate diagnosis and management can result in increased neurological injury.

Introduction

Central diabetes insipidus (DI) is characterised by a lack of anti-diuretic hormone (ADH) leading to inability to concentrate the urine and subsequent polyuria and hypernatraemia¹. Longterm therapy includes administration of desmopressin which acts on the distal tubules and collecting ducts of the kidney to increase water reabsorption.

Cisplatin is an alkylating agent used to treat a wide variety of solid tumours. As it leads to a reversible decline in glomerular filtration rate (GFR), pre-chemotherapy

hyperhydration is mandatory². A rarer side effect of cisplatin is renal salt wasting syndrome (RSWS) which leads to polyuria with subsequent volume depletion and renal salt losses. It has been described in 23 case reports since 1984³⁻⁸, of these only 5 occurred in children³⁻⁵.

This is the first report of central DI and cisplatin induced RSWS occurring simultaneously. We discuss the pathophysiology, the diagnosis and differential diagnosis and the therapeutic management with a review of the literature.

Case report

The two year old, previously healthy female was diagnosed with a suprasellar CNS-PNET after a 2 months history of lethargy, acute loss of vision and loss of weight. Surgical debulking of the tumor resulted in postoperative panhypopituitarism associated with hypernatremia, increased serum osmolality and decreased urine osmolality. The diagnosis of central DI was confirmed by an increase of urine osmolality after the administration of desmopressin. Subsequently she was started on regular desmopressin, thyroxine and hydrocortisone. Two weeks after surgery she received her first cycle of chemotherapy as per the Children's Oncology Group protocol ACNS0334 (Vincristine, Etoposide and Cyclophosphamide on day 1, Etoposide and Cyclophosphamide on day 2, Etoposide and Cisplatin on day 3). After day 2 of chemotherapy she developed fever and showed signs of sepsis with arterial hypotension (systolic blood pressure 50 mmHg), tachycardia (heart rate 180/min)

and elevated lactate (6.7 mmol/l). She was resuscitated with 0.9% saline (total of 60ml/kg) and started on noradrenaline (maximum dose 0.4 mcg/kg/min). She was commenced on empiric antibiotics and transferred to ICU. Cultures grew an enterobacter cloacae. Chemotherapy was continued the next day (day 3: Etoposide and Cisplatin). Hydrocortisone was increased to a stress dose and oral desmopressin was changed to the shorter acting intravenous vasopressin according to our local protocol. This consisted of 1 unit of vasopressin in 1 liter of 0.9% saline with the aim to replace the patients urine output + 10% hour by hour. A stable situation with an urine output of 4 – 8 ml/kg/hr and a serum sodium of 134 – 140 mmol/l was achieved. However, 36 hours after cisplatin administration her urine output increased abruptly to 27 ml/kg/hr and her serum sodium dropped to 121 mmol/l (normal range [NR] 135-145 mmol/l), (figure 1). The patient suffered a generalized seizure unresponsive to intravenous midazolam and needed endotracheal intubation. Her volume status appeared depleted with a central venous pressure (CVP) of 2 mmHg. She received 5ml/kg of 3% saline which acutely increased her sodium to 126 mmol/l. The urine analyses showed a urine-osmolality of 525 mosm/kg (NR, 50-1400 mosm/kg) and a urine-sodium of 212 mmol/l. She was extubated 24 hours later and appeared neurologically appropriate. Additionally, her serum creatinine increased from 30 to 50 μ mol/l (NR: 10 – 50 μ mol/l), which was attributed to be a combination of cisplatin nephrotoxicity and hypoperfusion injury caused by sepsis.

Due to the ongoing polyuria, natriuresis and urinary losses of other electrolytes with prior cisplatin administration the diagnosis of cisplatin RSWS was suspected. The subsequent clinical management with pre-existing DI proved to be extremely difficult. The vasopressin containing solution was changed to a continuous vasopressin

infusion. Urine output was replaced with 0.9% saline and the ongoing urinary losses of sodium with a continuous infusion of 3% saline (maximum dose 20ml/hr). Additionally she needed a continuous infusion of potassium chloride and many replacements of phosphate, magnesium, calcium and bicarbonate. Three weeks after cisplatin administration, she stabilized biochemically, with no need for electrolyte replacement and a normal urine output.

As per protocol, she commenced her second chemotherapy cycle (including cisplatin) four weeks later. Given the high risk nature of her tumor and concurrent septic episode we were hopeful she would tolerate the reexposure. Electrolytes and urine output were closely monitored and indeed, no significant imbalances occurred. She was discharged from ICU in good clinical condition without any additional neurological injury. She completed her therapy and remains in remission nine months post treatment.

Discussion

Children with intracranial disorders are at risk for electrolyte imbalances when the regulation of sodium and water homeostasis is affected⁹. (Table I).

Central Diabetes insipidus

Central DI is a known complication after CNS injury and causes hyponatremia due to lack of ADH leading to inability to concentrate the urine and subsequent free water loss. The incidence is high in patients undergoing pituitary surgery¹⁰ (15 to 36% depending on the surgical method) and is reported at 18% in one study in children with traumatic brain injury (TBI)¹¹.

Cerebral salt wasting syndrome

CSWS was first described by Peters *et al.* in 1950¹² and is characterised by renal salt loss and subsequent polyuria and volume depletion. The exact mechanism is poorly understood, however a disruption of neural input to the kidney and the direct elaboration of a circulating natriuretic factor are proposed¹³. The presumed diagnosis of CSWS has been reported in 110 subjects ≤ 18 years with intracranial surgery, meningoencephalitis and TBI¹³. CSWS has been intensively debated in the literature and some authorities find the term “cerebral” inappropriate¹⁴.

Syndrome of inadequate anti-diuretic hormone secretion

SIADH was first described by Schwarz *et al* in 1957¹⁵. Until recently, SIADH has been thought to be the most common cause of hyponatremia occurring after intracranial insults. The secretion of ADH is called inappropriate as it occurs in a euvolemic state which leads to further water retention and subsequent hyponatremia. Triggers for inappropriate ADH secretion include intracranial disorders, infections and numerous medications, including cisplatin.

Cisplatin nephrotoxicity and cisplatin induced RSWS

Cisplatin induced nephrotoxicity leads to a reversible reduction of the GFR in up to one third of treated patients². While wasting of electrolytes is common, renal wasting of salt is a rare side effect and is believed to occur as a result of cisplatin-induced damage of proximal tubular cells, the major site of electrolyte and water reabsorption, leading to electrolyte losses and polyuria⁵. RSWS has been reported with an incidence of $<1\%$ by Vassal *et al*⁵, while Hutchinson *et al* reported 10% ⁶. It has been described in 23 case reports, 5 of them in children³⁻⁸ (Supplemental table

1) In our case, we hypothesize that sepsis associated acute kidney injury might have precipitated cisplatin induced tubular toxicity.

Diagnosis and treatment

Diagnosing RSWS may be challenging and it may easily be misdiagnosed as SIADH, as both conditions share similar laboratory values¹⁴. The key to a correct diagnosis seems to be the patient's extracellular volume status, as patients with RSWS are hypovolemic while those with SIADH are euvolemic/hypervolemic. In addition, excessive urinary extraction of sodium (urinary sodium output exceeds sodium intake) and high percentage of fractional extraction of sodium are important indicators to diagnose RSWS.

The diagnosis of cisplatin induced RSWS in our patient was made according to the following criteria: Our patient had high urine sodium, her fractional sodium extraction rate was 6.1% and her sodium balance calculated on the day of severe hyponatremia showed the sodium output was 36.6g versus a sodium intake of 26.3g. We assume she was hypovolemic as her CVP was low.

It is important not to misdiagnose RSWS as SIADH as treatment is quite different.

Treatment of RSWS aims at restoration of euvolemia through water and salt administration while treatment of SIADH consists of fluid restriction.

This is the first report of DI combined with RSWS due to cisplatin. The accurate diagnosis and therapy is difficult but extremely important as misdiagnosis can lead to increased neurological injury.

Conflict of interest: The authors declare that they have no conflict of interest.

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233

234 **Figure 1: Urine output and serum sodium after cisplatin administration**

235 **Supplemental table 1: reported paediatric cases of cisplatin induced renal salt wasting**
236 **syndrome**

237

Table I. Differential diagnosis of renal salt wasting syndrome

	<i>Diabetes insipidus</i>	<i>SIADH</i>	<i>CSWS</i>	<i>Cisplatin induced RSWS</i>
Urine output	↑	↓	↑	↑
Serum Sodium	↑	↓	↓	↓
Urine Sodium	↓	↑	↑	↑
Serum osmolality	↑	↓	Normal/low	Normal/low
Urine osmolality	↓	↑	Normal/low	Normal/low
Volume status	Normal/low	↑	↓	↓

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Title:

Central Diabetes Insipidus and Cisplatin-Induced Renal Salt Wasting Syndrome: A Challenging Combination

Date:

2016-05-01

Citation:

Cortina, G., Hansford, J. R. & Duke, T. (2016). Central Diabetes Insipidus and Cisplatin-Induced Renal Salt Wasting Syndrome: A Challenging Combination. PEDIATRIC BLOOD & CANCER, 63 (5), pp.925-927. <https://doi.org/10.1002/pbc.25910>.

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