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Central diabetes insipidus induced by temozolomide: A report of two cases

Cédric Mahiat[1,*], Antoine Capes[2,*], Thierry Duprez[3], Nicolas Whenham[1,4], Lionel Duck[1] and Laura Labriola[2]

Abstract

Introduction: Central diabetes insipidus is a heterogeneous condition characterized by decreased release of antidiuretic hormone by the neurohypophysis resulting in a urine concentration deficit with variable degrees of polyuria. The most common causes include idiopathic diabetes insipidus, tumors or infiltrative diseases, neurosurgery and trauma. Temozolomide is an oral DNA-alkylating agent capable of crossing the blood-brain barrier and used as chemotherapy primarily to treat glioblastoma and other brain cancers.

Cases: Two men (aged 38 and 54 years) suddenly developed polyuria and polydispsia approximately four weeks after the initiation of temozolomide for a glioblastoma. Plasma and urine parameters demonstrated the presence of a urinary concentration defect.

Management: The clinical and laboratory abnormalities completely resolved with intranasal desmopressin therapy, allowing the continuation of temozolomide. The disorder did not relapse after cessation of temozolomide and desmopressin and relapsed in one patient after rechallenge with temozolomide.

Discussion: Our report highlights the importance of a quick recognition of this exceptional complication, in order to initiate promptly treatment with desmopressin and to maintain therapy with temozolomide.

Keywords

Diabetes insipidus, polyuria polydipsia, temozolomide, desmopressin

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Introduction

Central diabetes insipidus (DI) is a rare heterogeneous condition characterized by decreased release of antidiuretic hormone (ADH; also called arginine vasopressin or AVP), resulting in a urine concentration defect with variable degrees of polyuria. Underlying causes of central DI act at one or more of the sites involved in ADH secretion: the neurohypophysis, the hypothalamic osmoreceptors, the supraoptic or paraventricular nuclei, or the superior portion of the supraopticohypophyseal tract.[1] Prominent clinical features are polyuria, with or without nocturia, and polydipsia to compensate for urinary water losses triggered by increased -or in the high normal range- serum sodium concentration. However, moderate to severe hypernatremia can develop when thirst sensation is neurologically impaired or in case of restricted access to drinkable water. The most common causes include idiopathic DI, tumors or infiltrative diseases, neurosurgery, trauma, and brain malformations.[1,2] Hereditary (autosomal dominant or recessive) forms of central DI have also been reported.[3]

Temozolomide (TMZ) is an oral DNA-alkylating agent capable of crossing the blood-brain barrier and used primarily to treat high-grade brain cancers such as glioblastoma and other brain cancers.[4] Fatigue,

[1]Department of Oncology, Clinique Saint-Pierre, Ottignies, Belgium
[2]Department of Nephrology, Cliniques universitaires Saint-Luc, Brussels, Belgium
[3]Department of Medical Imaging, Cliniques universitaires Saint-Luc, Brussels, Belgium
[4]Department of Oncology, Cliniques universitaires Saint-Luc, Brussels, Belgium

*The first two authors contributed equally to this work.

Corresponding author:
Laura Labriola, Department of Nephrology, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, B-1200 Brussels, Belgium.
Email: laura.labriola@uclouvain.be

myelosuppression, rash, nausea and vomiting are the most frequently reported side effects.[5]

We report on two patients with glioblastoma presenting new onset central DI, concomitantly to the use of TMZ.

Cases

Case 1

A 38-year-old Caucasian man with a history of right temporooccipital glioblastoma diagnosed three months ago presented to the emergency department with nausea, inappetence, intense thirst and weight loss (6 kg over three weeks). The patient had undergone complete tumor resection and was treated by radiochemotherapy combining 60 Gy in 30 fractions over 44 days and oral TMZ 140 mg daily (75 mg/m^2/d) during radiotherapy. This treatment was followed by oral TMZ for 5 days in 28-day cycles (12 cycles planned), at the dose of 150 mg/m^2 in the first cycle and 200 mg/m^2 in subsequent cycles.

Three weeks after initiation of TMZ in September 2018, the patient suddenly developed polyuria (3500 mL/day) and polydipsia. He awoke 7–8 times per night to urinate and drank water. He reported nausea and vomiting for several days prior admission. Physical examination was normal. He was afebrile and normotensive. Initial laboratory studies revealed increased creatinine level [184.8 µmol/L (2.1 mg/dL), normal 52.8-114.4 µmol/L (0.6–1.3 mg/dL)] -a rise from 61.9 µmol/L (0.7 mg/dL) one month before admission-, serum urea 51 mg/dL (normal 15–50 mg/dL), normal blood cells count, and moderate inflammatory syndrome (C-reactive protein 5.8 mg/L, normal <5 mg/L). Serum sodium was at the upper limit of the normal range at 145 mmol/L (normal 135–145 mmol/L), and the other electrolytes were normal with potassium at 4.9 mmol/L (normal 3.5–5 mmol/L), and bicarbonate at 29 mmol/L (normal 22–29 mmol/L). Total serum calcium and phosphate were normal. Plasma and urine osmolality were 295 (normal range 280–300 mOsm/kg) and 172 mOsm/kg, respectively. Urinalysis showed a bland sediment, low-grade proteinuria [protein/creatinine ratio 0.25], and no glycosuria. Urine specific gravity was low (1.005). Renal ultrasound revealed normal-sized kidneys. Anterior pituitary function assessed at the time of diagnosis was normal (Table 1). A modified overnight water deprivation test could not be completed because the patient drank water during the night. However, morning laboratory tests showed plasma and urine osmolality at 295 and 170 mOsm/kg, respectively, and sodium at 145 mmol/L.

Treatment with intranasal desmopressin (dDAVP) was initiated. The dose was titrated progressively according to urine osmolality, until 30 mcg twice daily. Polyuria and polydipsia completely reversed. TMZ was not discontinued. Morning urine tests revealed a progressive increase in urine osmolality till 786 mOsm/kg (Figure 1(a)). Serum creatinine levels decreased over five weeks and returned within the normal range afterwards [0.9–1 mg/dL, (79.5–88.4 µmol/L)].

TMZ was completed 12 months after it was initiated. The dose was increased to 200 mg/m^2 in the second cycle, but was reduced to 150 mg/m^2 from cycle 3 because of leucopenia and thrombopenia. Intranasal dDAVP was tapered off over three months after discontinuation of TMZ. An overnight water deprivation test repeated four weeks after dDAVP cessation showed plasma and concurrent urine osmolality at 288 and 669 mOsm/kg, respectively, and serum sodium concentration at 140 mmol/L. Seven and four months after withdrawal of TMZ and dDAVP, respectively, the patient did not experience a relapse of the symptoms of DI and laboratory tests were normalized.

Sequential whole brain magnetic resonance imaging (MR) examinations, performed in the frame of the tumor work-up, excluded tumor involvement of hypothalamus and/or pituitary stalk/gland (Figure 2). Disappearance of the physiological 'bright spot' of the neurohypophysis on pre-contrast T1-weighted MR images could not be assessed since the standardized MR protocol for glioblastoma monitoring did not include pre-contrast imaging focused on the pituitary gland. Patient 1 gave written informed consent for publication of patient information and images.

Case 2

A 54-year-old Caucasian man with a history of right frontotemporal glioblastoma diagnosed two months ago presented with polyuria and polydipsia. Complete tumoral excision had been followed by external radiotherapy (60 Gy in 30 fractions over 43 days) and concomitant chemotherapy with oral TMZ (160 mg/day), followed by oral TMZ 5 days/28 (6 planned cycles, 150 mg/m^2 in the first cycle and 200 mg/m^2 in subsequent cycles).

One month after initiation of TMZ, the patient developed polydipsia (approximately 4 L/day of fluid intake), polyuria (without nocturia) and generalized weakness. Physical examination was unremarkable. Laboratory testing suggested a urinary concentrating defect: serum sodium 145 mmol/L (normal 135–145 mmol/L), plasma osmolality 296 mOsm/kg (normal 280–300 mOsm/kg), concurrent urine osmolality 230 mOsm/kg and urine specific gravity 1.006.

Table 1. Anterior pituitary function.

Hormones (normal range)	Case 1	Case 2
TSH (0.27–4.2 U/L)	1.36	0.71
Free T4 (12–22 pmol/L)	19.9	14.5
Total testosterone (11.4–27.9 nmol/L)	13.2	10.91
Prolactin (4–15 μg/L for males; 4–23 μg/L for females)	12.8	6.4
Morning cortisol (130–500 nmol/L)	356.7	–
IGF-1 (102–292 ng/mL)	193.6	236

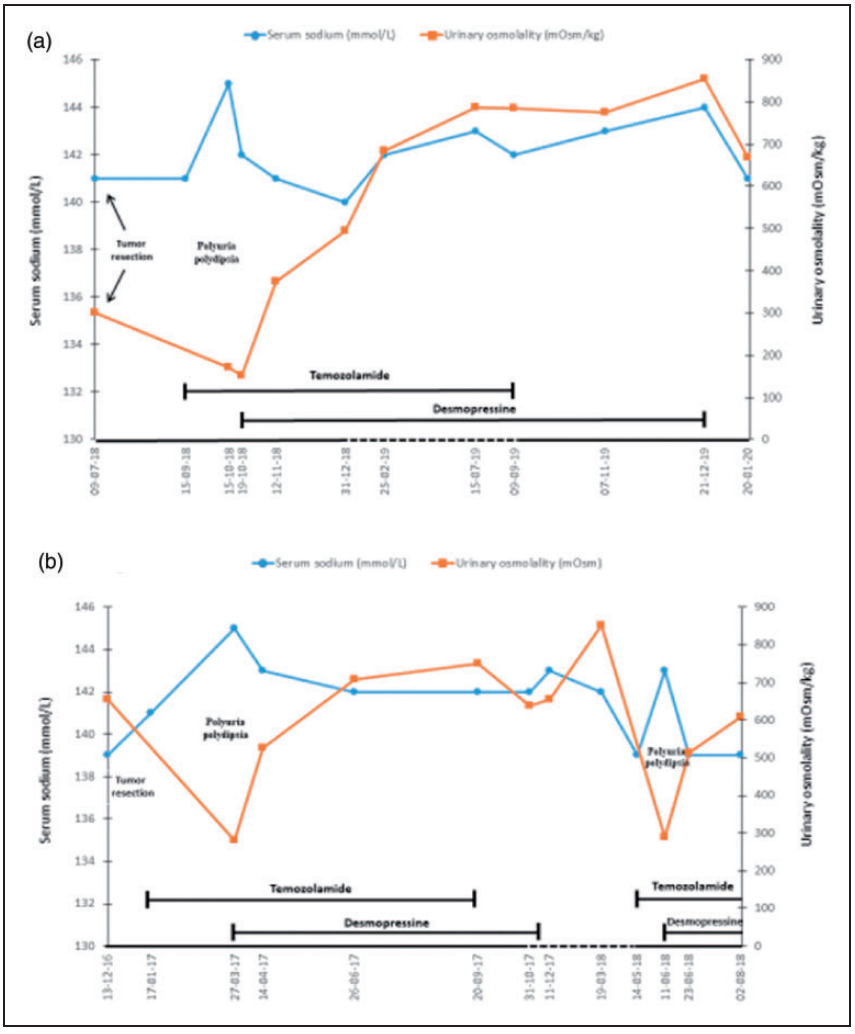

Figure 1. Changes in serum sodium (mmol/L) and urinary osmolality (mOsm/kg) in Patient 1 (a) and Patient 2 (b). The left y-axis indicates serum sodium concentrations, while the right y-axis indicates urinary osmolality. The x-axis indicates time starting from the tumor resection. The dotted line on the X axis indicates a smaller scale between end of December 2018 and September 2019 (a) and between end of October 2017 and May 2018 (b).

Serum creatinine was 80.9 μmol/L (0.91 mg/dL) [CKD-EPI estimated glomerular filtration rate (*e*GFR) 95 mL/min/1.73m^2]. Serum calcium was in the normal range. Urine sediment was bland, and there was no glycosuria or proteinuria. As depicted in Table 1, anterior pituitary function tests at the time of diagnosis were normal. Testosterone levels were slightly below the normal range, which suggested primary hypogonadism due to age.

Intranasal administration of dDAVP (10 mcg twice daily) resulted in immediate symptoms relief. Subsequent laboratory tests showed a serum sodium

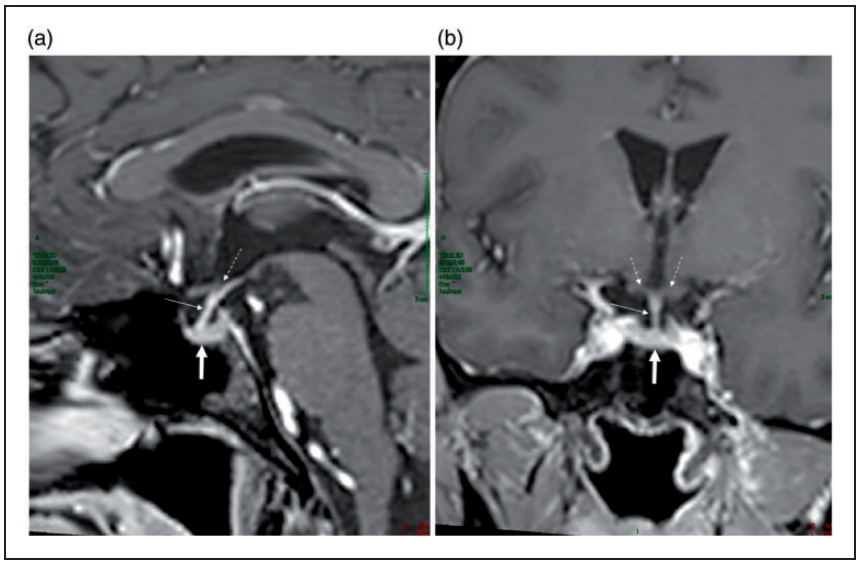

Figure 2. Magnetic resonance MR examination of Patient 1. Reformated views from high-resolution post-contrast 3 D T1-weighted volume (voxel size 1 mm^3 isotropic). (a) Mid-sagittal view showing normal pituitary gland (thick arrow), pituitary stalk (thin arrow), and infundibular recess (dotted arrow). (b) Coronal view confirming unremarkable gland (thick arrow) and stalk (thin arrow) together with normal hypothalamus (between dotted arrows).

concentration at 141 mmol/L, plasma osmolality at 288 mOsm/kg, and urine osmolality at 561 mOsm/kg (Figure 1(b)). TMZ was not discontinued and was completed 6 months after it was initiated. DDAVP was withdrawn 2 months after TMZ termination. Polydipsia and polyuria did not relapse. Laboratory parameters obtained three weeks after cessation of dDAVP revealed a serum sodium concentration at 142 mmol/L, serum osmolality at 290 mOsm/kg and concurrent urine osmolality at 654 mOsm/kg. Sequential brain MR neuroimaging aiming at monitoring tumor changes allowed to exclude infiltration of the neuropituitary axis similarly as in the previous patient (not shown). The posterior pituitary bright spot on pre-contrast T1-weighted images was not visible prior, during or after TMZ therapy.

Six months after TMZ cessation the patient underwent surgical re-intervention for local tumor recurrence. Treatment with oral TMZ was started again (5 days/28, 150 and 200 mg/m^2 in the first and subsequent cycles, respectively). Four weeks later, intense thirst and polyuria (3–4 L/day) recurred. Plasma and urine osmolality were 293 and 290 mOsm/kg, respectively, and serum sodium concentration was 143 mmol/L. DDAVP was immediately initiated (10 mcg twice daily), resulting in a rapid symptom relief. Two months later, morning plasma and urine osmolality were concomitantly measured at 285 and 609 mOsm/kg, respectively (Figure 1(b)).

The patient died from tumor progression six months later.

Discussion

We report two cases of central DI associated to treatment with TMZ. The strength of association is strong because clinical and biological abnormalities correlated well with both the initiation and discontinuation of TMZ. Indeed, both patients presented with a urine concentrating defect developing 3–4 weeks after initiation of daily TMZ. In both cases, clinical and laboratory abnormalities reversed soon after initiation of dDAVP and did not relapse over 7–9 months after TMZ discontinuation. Furthermore Patient 2 experienced a recurrence of the same clinical and laboratory picture one month after rechallenge of TMZ on a less intensive dosing strategy, and his clinical and laboratory parameters again corrected after re-treatment with dDAVP. According to the Naranjo algorithm, this adverse reaction is definitely associated with temozolomide use (score 9).[6]

At presentation, the differential diagnosis of polyuria-polydipsia syndrome included solute (osmotic) diuresis, primary polydipsia, central DI and nephrogenic DI. Osmotic diuresis in the setting of hyperglycemia caused by steroids prescribed for tumor or treatment-associated edema was rapidly excluded in both patients because of normal serum glucose levels and no glycosuria. Primary polydispsia was also excluded since serum sodium concentration was at the high normal level in both cases (145 mmol/L). Low urine osmolality levels in the first urine sample of the morning (<300 mOsm/kg in both patients, even <200

mOsm/kg in Patient 1) pointed toward a central or nephrogenic DI. An overnight fluid deprivation test followed by administration of exogenous desmopressin, in order to determine the type of DI, could be performed in none of both patients at the time of the diagnosis. However the complete reversal of polyuria and polydipsia, together with the clear rise in urine osmolality and the decrease in serum sodium concentration and plasma osmolality after dDAVP, strongly suggested central DI.[7] Common causes of nephrogenic DI -as long-term lithium use, obstructive uropathy or persistent hypercalcemia[8]- were absent in both patients. Furthermore, no signs of tubular injury were present. Admittedly, most patients with partial nephrogenic DI may also have an increase in urine osmolality after dDAVP administration, due to a partial resistance to ADH. However urine osmolality levels rose more than two times after dDAVP administration in our two patients, and remained well above 300 mOsm/kg, which argues against the diagnosis of partial nephrogenic DI.[9]

The pathogenesis of TMZ-induced central DI is unclear, and may involve either the production, storage or secretion of ADH from the neurohypophysis. Several mechanisms have been hypothesized, i.e. dysruption of actin cytoskeleton in neuroendocrine cells, and modification of purinergic receptor signaling in magnocellular neurons of the supraoptic nucleus by TMZ, resulting in an impairment of oxytocin and ADH release.[10,11] Interestingly, central DI was never reported in association with dacarbazine, a prodrug of the same active cytotoxic metabolite as TMZ which do not cross the blood-brain barrier.

Absence of hypersignal intensity within the neurohypophysis (bright spot) on pre-contrast T1-weighted MR images is the standard radiological sign of 'idiopathic' central DI after the exclusion of inflammatory or neoplastic involvement of the neurohypophyseal axis.[12,13] In our both patients a standardized MR protocol for high-grade glioma monitoring was serially performed which did not include sagittal pre-contrast T1-weighted sagittal views focused on the pituitary gland, resulting in a loss of the specific sign of the 'bright spot' disappearance. On the other hand, T1-hyperintensity of the neurohypophysis revealing the presence of lipophilic ADH-containing granules[12] may be absent in up to 20–30% normal individuals.[13] Crucially MR examinations unequivocally allowed the exclusion of hypophyseal involvement by the neoplastic process or any other pathologic process (Figure 2).

Admittedly, radiation therapy (undergone by both patients for their malignancy) could have caused a lesion in the hypothalamic/pituitary region. However, although anterior pituitary abnormalities after therapeutic cranial irradiation for extrasellar brain tumors are common,[14] DI has never been reported.[15,16] Moreover, there is a clear temporal correlation between TMZ administration-cessation and the onset-reversal of the clinical picture in our two patients, and, in Patient 2, between the rechallenge of TMZ and the recurrence of DI, which reinforces the hypothesis of the causative role of TMZ on the pathogenesis of central DI.

TMZ received accelerated approval by the US Food and Drug Administration in January 1999 for the treatment of anaplastic astrocytomas,[17] and then in March 2005 for newly diagnosed glioblastoma multiforme concomitantly with radiotherapy.[18] Despite its long-term and common use to treat brain tumors, there has been only one report of TMZ-induced DI.[19] Faje et al. reported in 2013 on two patients with new central DI associated with TMZ. In both cases, DI developed two months after starting TMZ, and resolved after treatment with dDAVP. Using the electronic registry database from their institution, the authors identified three additional potential cases of TMZ-induced DI (aged 44–49 years) among 1545 patients treated with TMZ.[19] Two out of 3 patients developed polyuria and polydispsia 2–3 months after initiation of TMZ, including one patient with mild acute renal failure. In two patients polyuria and polydipsia spontaneously resolved although TMZ was continued. Only one patient received dDAVP. Whole-brain MR did not show any evidence of mass or infiltrative lesion in the three patients. The authors thus conclude that the prevalence of TMZ-induced DI was 0.3% in their survey. Using our institution's pharmacy electronic data, we identified 721 patients treated with TMZ at Cliniques universitaires Saint-Luc (January 2006–April 2020). Thus the prevalence in our survey is 0.28%, very similar to that reported by Faye et al.

To the best of our knowledge there has not been any other case of TMZ-induced DI reported so far. DI appears to be thus a rare side effect of TMZ. However, since the occurrence of paucisymptomatic cases has never been reported, the current prevalence of this complication might be underestimated. Interestingly, DI occurred during or after the first, more intensive, phase of TMZ treatment -i.e. daily doses- in our both patients, and also in the prior reported two cases.[19] However, DI recurred in Patient 2 on a less intensive dose schedule, which argues against a dose-dependent effect.

In conclusion, we report two cases of new central DI associated to the use of TMZ. Our patients fulfilled all clinical/biological criteria associated with this condition. Importantly, clinical picture and laboratory parameters responded well to the administration of desmopressin, a vasopressin analog, allowing the continuation of TMZ. The disorder did not relapse after

cessation of TMZ and desmopressin. Central DI appears to be a rare side effect associated to TMZ, but its current prevalence may be underestimated. Our cases highlight the need of a rapid recognition of this complication of which prompt treatment can significantly improve patients' quality of life while maintaining the therapy by TMZ.

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ORCID iDs

Cédric Mahiat https://orcid.org/0000-0002-7253-8235
Laura Labriola https://orcid.org/0000-0003-4133-881X

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