

Nephroquiz (Section Editor: M. G. Zeier)

Transient nephrogenic syndrome of inappropriate antidiuresis

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Background

Chronic hyponatraemia is commonly caused by inappropriate secretion of antidiuretic hormone; the entire syndrome is commonly known as SIADH. Tumors are a well-known cause and when removed the condition can be cured. Most annoying is the outcome when a perfectly plausible cause is rectified and the SIADH refuses to ‘go away’. We were recently confronted with this state of affairs.

Case

The patient is a 56-year-old man who entered the hospital because of hyponatraemia. He observed problems with short-term memory, gait disturbances, and had fallen while going downstairs. He also claimed attention deficits and visual disturbances. He had been presented to his primary care physician who observed a low serum Na⁺ (102 mmol/L) and referred him for further diagnostic studies. The patient otherwise enjoyed stable health. He had undergone stent placement for coronary disease but had normal cardiac function. He ingested simvastatin and aspirin. Aside from some ibuprofen after a tooth extraction some weeks earlier, he had ingested no other tablets. He denied weight loss, any gastrointestinal symptoms and had not observed cough or shortness of breath. His blood pressure was 140/85 mmHg, heart rate 68/min. He was oriented in all spheres; his tandem walking and Romberg testing were slightly unstable, he had no oedema, and no other pertinent findings. The chest roentgenogram was normal. Computerized tomography suggested the presence of a gastric mass, which after an extensive workup, was resected. The lesion turned out to be a gastrointestinal stromal tumour (GIST). Laboratory findings are given in Table 1.

We reasoned that this euvolemic patient had syndrome of inappropriate antidiuretic hormone (SIADH) related to the GIST. However, post-operatively the serum Na⁺ decreased to 117 mmol/L and the preoperative anti-diuretic hormone (ADH) measurement from admission was returned at 1.3 ng/L, a low value. The patient was discharged with tolvaptan 7.5 mg/day. We had occasion to test him briefly during tolvaptan treatment. With a serum

Na⁺ of 142 mmol/L he ingested 1.5 L water over 20 min. His serum Na⁺ stayed stable at 140 mmol/L, while his urinary osmolality fell to 101 mOsm/L with Na⁺ 14 and K⁺ 5 mmol/L.

Make your diagnosis: Nephrogenic syndrome of inappropriate antidiuresis ?

We first double checked with our ADH laboratory (Limbach Laboratory, Heidelberg, Germany). The laboratory has superb standards and they have a very good track record of reliability. We were faced with SIADH in the absence of elevated ADH values, which calls to mind the nephrogenic syndrome of inappropriate antidiuresis (NSAID) [1]. NSAID is a rare, recently recognized, disorder in water balance affecting not only children but also adults. The mechanism involves a gain-of-function mutation in the arginine vasopressin receptor type 2 gene (*AVPR2*) that causes constitutive activation of the receptor. The clinical manifestations of NSAID are indistinguishable from SIADH [2]. Of course, our GIST was a very attractive candidate for the latter; however, we had to relinquish that possibility. Subsequent *AVPR2* sequencing revealed no mutations in that gene. We were ‘clueless’ but could continue to treat our patient with tolvaptan (€80 per tablet).

This frustrating state of affairs continued several months. We had a patient with evident NSAID without a mutation in *V2R*, who gratifyingly enough profited from a very expensive treatment. The GIST made no reappearance. As a matter of fact, the oncologists declared the patient as cured. We are aware of a review by Robertson [3] that classified SIADH patients into four different groups. Some had continually elevated ADH values, while some had elevated ADH values only when stimulated with water restriction. Others still had oddly low ADH values even in the presence of hyponatraemia, as was the case here. Ten months after our patient was declared ‘tumour-free’, tolvaptan was withdrawn and he was retested. He was offered 2 L of water to drink and his serum Na⁺ promptly sank to 130 mmol/L with a urine osmolality of 585 mOsm/L, Na⁺ 181 mmol/L, K⁺ 28 mmol/L. Thus, the free water clearance was still negative, indicating that the driving mechanism had not resolved.

Recently, almost 2 years after the initial presentation, the patient presented with the comment: ‘Hey doc, I don’t

Table 1. Patient data

	Before admission	Admission	Discharge ^a
Serum Osm (mOsm/L)	212	263	300
Serum Na ⁺ (mmol/L)	102	124	140
Serum K ⁺ (mmol/L)	4.6	4.3	4.6
Urine Osm (mOsm/L)	650	784	794
Urine Na ⁺ (mmol/L)	–	184	54
Urine K ⁺ (mmol/L)	–	74	78

^aAfter water restriction and furosemide.

think I need this expensive stuff anymore!’ He had since discontinued tolvaptan. We tested him again with 1.6 L of water given over 20 min and found that his serum Na⁺ which began at 133 mmol/L actually increased to 135 mmol/L, while his urine osmolality was reduced from 377 mOsm/L to 130 mOsm/L with urine-Na⁺ at 18 and K⁺ at 8 mmol/L. He now exhibited a positive free water clearance. Under these circumstances, the ADH level was <1.0 ng/L. We cannot incriminate simvastatin, since this drug was given throughout, as was aspirin. Given the negative V2R sequencing data, NSIAD seems to be unlikely. However, the long lag time between GIST resection and normalization of the free water clearance is remarkable and unusual for malignancy-associated SIADH. Thus, the GIST could also be an unrelated accidental finding. The response to

tolvaptan would support a diagnosis of SIADH; however, tolvaptan may induce some response even in patients with NSAID by altering channel conformation. Carboxy-terminal proarginine vasopressin (copeptin) is now being offered as a surrogate and adjunctive marker of ADH release [4]. Unfortunately, the material is not absolutely stable and we could not measure it in our earlier samples. We conclude that ‘whatever it was’ is going away.

Conflict of interest statement. None declared.

References

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