More than just Diabetes Insipidus

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Introduction

Cranial Diabetes Insipidus (CDI) is defined as the inability to concentrate urine due to deficient secretion of Anti-Diuretic Hormone (ADH). The majority of cases are idiopathic but can be caused by intracranial tumours, infiltrative disease and trauma. We report a case where CDI was only part of a more complex disease entity.

Case Report

A 54 year old gentleman with no past medical history initially presented to his GP with symptoms of increased urinary frequency, urgency and nocturia. Examination by his GP was unremarkable, except for a slightly enlarged prostate. Further blood tests (serum prostate specific antigen, fasting serum glucose) and urine microscopy culture and sensitivities were all normal. He was treated for benign prostate hypertrophy and started on Tamsulosin.

Unfortunately this failed to alleviated his symptoms therefore he was referred to the Urology team. When asked to monitor his fluid input and output, this revealed he was drinking in excess of 6 litres of fluid per day, hence he was referred to our team.

On review in the Endocrine Clinic, this gentleman had:

- A 6 month history of polyuria and polydipsia
- No previous history of head trauma / cranial surgery
- No history of headaches
- No symptoms or signs of any visual field defects
- Alcohol intake of 4-6 pints of beer daily

He was advised to reduce his alcohol intake and keep a diary of his fluid input and output.

Investigations

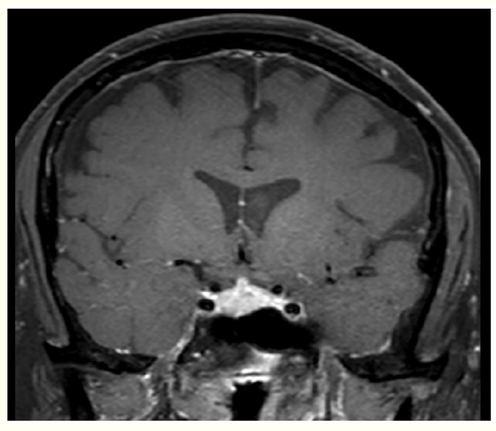
At his second clinic visit our patient had significantly reduced his alcohol intake to 10pints of beer per week but still complained of nocturia, passing **>3500ml urine overnight**. His investigations are as follows:

Na 144 (133-146 mmol/L)	Bili 27 (<21 umol/L)	TSH 4.32 (0.27-4.2 mU/L)
K 4.5 (3.5-5.3 mmol/L)	ALP 118 (30-130 U/L)	fT4 17.2 (12-23 pmol/L)
Ur 3.8 (2.5-7.8 mmol/L)	ALT 83 (0-41 U/L)	fT3 5.1 (4-7.8 pmol/L)
Cr 110 (65-111 umol/L)		
Glucose 5.8 mmol/L	Cortisol 556 nmol/L	Prolactin 266 (0-500 mIU/L)
HbA1c 31 mmol/mol		

Serum osmolality	300 mmol/kg (275-295)
Urine osmolality	147 mmol/kg
Urine osmolality (after overnight water deprivation)	161 mmol/kg

We therefore proceeded to do a **Formal Water Deprivation Test**

Time	Urine osmolality (mmol/kg)	Serum osmolality (mmol/kg)	
09:00	148		
09:30		296	
12:00	146		
12:30		299	
15:00	171		
15:30		305	
16:00	194		
16:30		304	**DDAVP given**
17:30	273		
18:00	346		
19:00	378		
20:00	404		



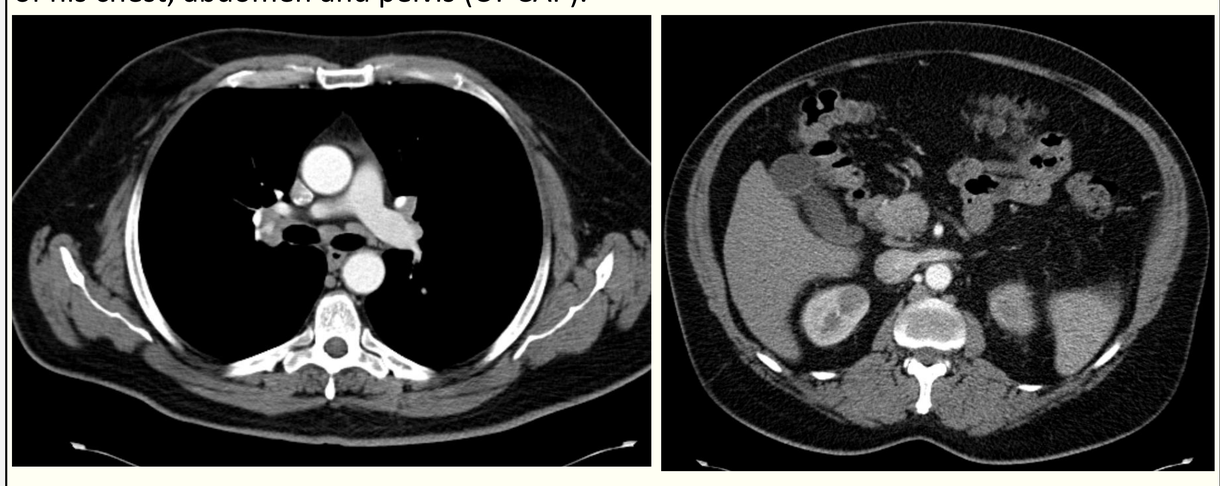
The water deprivation test above are consistent with a diagnosis of **partial CDI**.

He subsequently went on to have an MRI pituitary scan. This was reported as showing a 'thickened infundibulum and pituitary gland, classical for lymphocytic hypophysitis'.

He was therefore started on **Desmopressin 100micrograms TDS** with a good clinical response.

Meanwhile, the plot thickens…

Our patient attended the Accident and Emergency department at another Trust complaining of chest pain. A chest radiograph done as part of the work-up showed hilar lymphadenopathy. This was further investigated with a computerised tomography scan of his chest, abdomen and pelvis (CT CAP).



CT CAP revealed

- Extensive mediastinal, para-aortic and para-iliac lymphadenopathy, up to 22mm.
- Suspicious low density lesions of both the left and right kidneys
- Highly suspicious features suggestive of retroperitoneal fibrosis.

Subsequently this gentleman was reviewed by the Respiratory team where investigations for sarcoidosis were 'inconclusive'.

In view of the 'suspicious lesions' on both kidneys he was also referred back to the urologists where a renal biopsy was performed. This showed **Tubulointerstitial Nephritis**

In summary this gentleman had accumulated the following:

1. Diabetes Insipidus
2. Evidence of lymphocytic hypophysitis on MRI pituitary
3. Extensive lymphadenopathy
4. Retroperitoneal fibrosis
5. Lesions on both kidneys showing Tubulointerstitial Nephritis on biopsy

Could there be a unifying diagnosis?

A diagnosis of Immunoglobulin-G4 Related (IgG4 related) Disease was proposed.

This was confirmed by

- High plasma IgG4 levels 3.07 (0 -1.3 g/L) and
- IgG4 positive staining on renal biopsy

Management

Upon diagnosis he was referred to a tertiary centre for further management of his IgG4 related disease. At this point he had developed new symptoms of fatigue, weight loss (2 stones in 3 months), reduced libido and erectile dysfunction.

Further blood tests revealed he had developed **renal failure**: Urea 28.4, Creatinine 518 (normal 3 months ago). There was also evidence of **testosterone insufficiency**: total Testosterone 0.5 (6.7-31 nmol/L), LH 1 (1-8 IU/L), FSH 2.6 (1-10 IU/L).

He was commenced on prednisolone 40mg daily for 4 weeks, then reducing doses to a maintenance of 10mg daily. He was also started on Testogel 1 sachet daily.

Progress

This gentleman's renal function significantly improved with prednisolone treatment (Cr 170 within the first month of starting steroids). His renal function is now back to baseline, on a maintenance dose of 10mg prednisolone daily. He continues on Testogel and Desmopressin. In the long term he is keen to come off the steroids and treatment with Azathioprine is being considered.

Conclusion

IgG4-related disease is an immune-mediated condition characterised by elevated serum IgG4 levels and infiltration of tissues by IgG4 plasma cells. It can affect almost every organ system in the body [1,2]. CDI is a rare feature of this disease and even more uncommonly the presenting symptom. First reported in the literature in 2008 [3], recent studies suggest its prevalence has been underestimated [4]. Our gentleman initially presented with features of DI but subsequently showed evidence of multi-organ involvement. Interestingly he was under the care of three specialists, all from different Trusts, prior to getting this unifying diagnosis.

This case highlights the importance of considering this multisystem disease when diagnosing CDI as it has significant implications on management. It also emphasises the need for a multi-disciplinary approach in investigating and managing these patients.

References: [1] John H. *et al*. IgG-4 Related disease. New England Journal of Medicine,2012;366:539-551. [2] Kamisawa T. *et al*. IgG4-related Disease. The Lancet,2014;385(9976):1460-1471. [3] Isaka H. *et al*. A case of IgG4 related multifocal fibrosclerosis complicated by diabetes insipidus. Endocrine Journal,2008;5(44):723-728. [4] Bando H. *et al*. The prevalence of IgG4 related hypophysitis in 170 consecutive patients with hypopituitarism and/or central diabetes insipidus and review of the literature. European Journal of Endocrinology, 2014;170:161-172.

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