When looking at the individual studies, the C allele is present at similar frequencies within the two UK Caucasian populations (75-1% and 74-8%), whereas the frequency of the C allele is higher within the USA study (82%) and lower within the Korean study (71%). This difference is also mirrored by the frequencies of the CC genotypes, where the CC genotype is reported to be 55-3% and 54-7% prevalent within the UK Caucasian populations, compared with 65% frequency within the USA population and 50% within the Korean population. A meta-analysis using the Mantel–Haenszel methods, where the ORs from each of the four studies are weighted (θ), produces an overall pooled OR (θpooled) of 1-18, with a 95% CI of 0-21–4-88. An elevated OR, crossing 1 and with such a wide 95% CI, is unlikely to be significant, and this result is likely to reflect a random chance event or mismatching between the different populations examined.

Meta-analysis of only the data from the two UK Caucasian data-sets, again using the Mantel–Haenszel methods, produces a θpooled of 1-09, with a 95% CI of 0-96–1-24. Furthermore, assuming a recessive model, by comparing the CC genotype to both the CT and TT genotypes combined, no association of the CC genotype can be found (χ² = 2-848, P = 0-092) within the pooled UK Caucasian datasets. This meta-analysis can therefore rule out an effect of the size of 1-22 reported for all four studies within the study by Jacobson et al., however, a minor effect of OR = 1-09 within the UK Caucasian population cannot be completely excluded. Notably, a dataset of 5500 GD subjects and 5500 matched control subjects would be needed to have 65% frequency within the USA population and 50% within the Korean genotypes, where the CC genotype is reported to be 55-3% and 71-7%. This difference is also mirrored by the frequencies of the CC genotypes within the USA study (82%) and lower within the Korean study (75-1% and 74-8%), whereas the frequency of the C allele is higher within acute severe hypernatraemia caused by central diabetes insipidus

A 55-year-old female was brought to the Harbor-UCLA Medical Center emergency department with altered mental status over a few days. On the day of admission, the patient became somnolent with increased urine output despite decreased oral intake. There was no history or evidence of alcoholism, renal disease, malnutrition or episodes suggesting prolonged hypoxia. On initial examination, the patient was hypotensive with a blood pressure of 91/57 mmHg and a heart rate of 86 beats/min. She was orientated only to self and was unable to follow instructions for a full neurological assessment. Initial serum sodium level was 172 mmol/l (reference range 136–144 mmol/l), urea nitrogen was 8-9 mmol/l and glucose 7-0 mmol/l. The diagnosis of central diabetes insipidus was made as the patient had inappropriately low urine osmolality of 230 mOsm/kg with a high serum osmolality of 370 mOsm/kg (reference range 278–305 mOsm/kg) on presentation. The patient was aggressively fluid resuscitated over a 3-h period with 12 l of normal saline and a high serum osmolality of 370 mOsm/kg (reference range 278–305 mOsm/kg) on presentation. The patient was aggressively fluid resuscitated over a 3-h period with 12 l of normal saline and was administered desmopressin (DDAVP) 10 µg intranasally. Two hours later she was given another dose of DDAVP 50 µg intranasally, which resulted in her urine osmolality increasing from 230 to 444 mOsm/kg. She remained hypotensive with a blood pressure of 86/44 mmHg and a heart rate of 84 beats/min and was subsequently intubated for acute respiratory distress and developed a brief episode of bradycardia and pulseless electrical cardiac activity, which resolved with atropine.

Eight hours after admission adrenal function evaluation showed a low serum cortisol of 210 nmol/l (AM reference range 220–660 nmol/l) and ACTH 167 pmol/l (reference range 154–1123 pmol/l) while under acute stress and a corticotrophin stimulation test was
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not performed. She was then treated with high-dose steroids (hydrocortisone 100 mg IV every 8 h) for possible adrenal insufficiency. Within 21 h, the patient’s blood pressure returned to 110/60 mmHg and serum sodium and osmolality levels decreased to 154 mmol/l (change of −18 mmol/l) and 311 mOsm/kg, respectively. At 48 h, the serum sodium level was 143 mmol/l with a serum osmolality of 291 mOsm/kg (−29 mOsm/kg from admission). Two days after admission, baseline anterior pituitary function showed that her serum FSH and LH levels were low for a postmenopausal woman at < 1·2 and 3·8 IU/l, respectively (reference ranges for postmenopausal women both > 40 IU/l).

A magnetic resonance imaging (MRI) study performed on hospital day 9 showed a contrast-enhancing 3 mm mass-like focus involving the inferior hypothalamus bilaterally and thickening of the base of the pituitary stalk suggestive of a granulomatous process, primary tumour or metastasis. In addition, there was abnormal signal intensity in the bilateral cerebellar peduncles and splenium of corpus callosum without affecting the pons suggesting a possible demyelination syndrome or myelinolysis (Figs 1a,b and 2a). By day 8, the patient’s neurological examination was normal. MRI abnormalities of myelinolysis usually show only partial resolution as patients improve clinically. On day 11, a repeat Cortrosyn stimulation test showed normal response (serum cortisol increased from a baseline 254 mmol/l to 690 and 855 mmol/l at 30 and 60 min, respectively) and her hydrocortisone was gradually withdrawn. Further endocrine testing on day 19, before her discharge from hospital, showed normal serum PRL, basal GH IGF-I levels (GH stimulation test was not performed), and thyroid function tests. The patient continued to improve on DDAVP 20 µg in the morning and 30 µg in the evening intranasally. A follow-up outpatient MRI of the head 1 and 2 months later showed that the small lesion with bright enhancement at the base of pituitary was no longer visible and that the increased signals in the bilateral cerebellar peduncles and splenium of corpus callosum had improved substantially (Figs 1c–f and 2b). When the patient’s DDAVP was temporarily withdrawn for testing, her urine osmolality decreased to 90 mOsm/kg and serum osmolality increased to 319 mOsm/kg, indicating that she had persistent diabetes insipidus.

There are two distinct and unusual features in this patient. First, based on the clinical presentation of diabetes insipidus, the presence of anterior pituitary hormone insufficiency, the initial radiological picture of a thickened pituitary base mimicking a mass and the subsequent resolution of the hyperintense signal and focal thickening of stalk, the patient probably had lymphocytic infundibulo-hypophysitis.1,2 Lymphocytic hypophysitis is typically observed in

Fig. 1 Axial MR images using a FLAIR sequence. There was abnormal signal intensity within the splenium of the corpus callosum and cerebellar peduncles (a and b). At 1 month (c and d) and 2 months follow-up (e and f), there was progressive improvement.
women during late pregnancy or in the postpartum period but may be seen at any age or gender. This process generally affects the adenohypophysis and only in 20–30% of the patients is the neurohypophysis involved, which was not the situation here.

Second, the patient’s extrapontine myelinolysis was probably secondary to the acute severe hypernatraemia as the patient presented with acute mental status changes. A slow onset of hyperosmolality does not result in myelinolysis because the brain protects against osmotic stress by accumulating electrolytes and organic solutes to ensure isotonicity with respect to serum. Extrapontine myelinolysis has been reported to be associated with severe acute hypernatraemia usually in the presence of other medical problems such as alcoholism (Marchiafava–Bignami), severe burns, hyperglycaemia and disequilibrium syndrome. Extrapontine and pontine myelinolysis frequently coexist and have identical pathological changes in the two anatomical sites. The pathogenic basis is thought to be rapid intracellular brain dehydration resulting in unravelling of the myelin sheath away from the axons. This patient was unusual as there are few published reports of extrapontine myelinolysis caused by central diabetes insipidus resulting in severe acute hypernatraemia in children but not in adults. We also recognize that the rapid rate at which serum sodium correction occurred from hypernatraemia to normonatraemia while she was being resuscitated in the emergency room might have contributed to her clinical situation. However, correction of hypernatraemia has not been reported to be association with myelinolysis. Furthermore, the patient was never hyponatraemic during her hospital course, nor was there evidence of brain oedema in the MRI, indicating that the myelinolysis was likely to be secondary to the acute hypernatraemic state and not due to the electrolyte changes that occurred during resuscitation on admission. It should be emphasized that the common cause of pontine myelinolysis is the rapid reversal of hypernatraemia (rates exceeding 10–15 mmol/l/24 h) producing brain cell shrinkage resulting in neurological damage, and methods to avoid this iatrogenic complication are through a slow correction rate of serum sodium.

This is the first reported case of an adult female presenting with central diabetes insipidus that was probably due to lymphocytic neuroinfundibulo-hypophysitis and radiological evidence of extrapontine myelinolysis secondary to acute severe hypernatraemia.

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References


More on the measurement of normal testosterone levels: comments on the Barrett–Connor commentary

We appreciate Dr Barrett-Connor’s commentary on our recent paper using data from the Massachusetts Male Ageing Study (MMAS).