

Osmotic demyelination syndrome in a patient with Noonan syndrome and anterior hypopituitarism

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Summary

Severe hyponatremia and osmotic demyelination syndrome (ODS) are opposite ends of a spectrum of emergency disorders related to sodium concentrations. Management of severe hyponatremia is challenging because of the difficulty in balancing the risk of overcorrection leading to ODS as well as under-correction causing cerebral oedema, particularly in a patient with chronic hypocortisolism and hypothyroidism. We report a case of a patient with Noonan syndrome and untreated anterior hypopituitarism who presented with symptomatic hyponatremia and developed transient ODS.

Learning points:

- Patients with severe anterior hypopituitarism with severe hyponatremia are susceptible to the rapid rise of sodium level with a small amount of fluid and hydrocortisone.
- These patients with chronic anterior hypopituitarism are at high risk of developing ODS and therefore, care should be taken to avoid a rise of more than 4–6 mmol/L per day.
- Early recognition and rescue desmopressin and i.v. dextrose 5% fluids to reduce serum sodium concentration may be helpful in treating acute ODS.

Background

Severe hyponatremia increases morbidity and mortality. Management of hyponatremia depends on the chronicity of hyponatremia to avoid the risk of osmotic demyelination syndrome (ODS) from overly quick correction while balancing the potential detrimental effects of severe hyponatremia which itself can lead to seizures, arrhythmia and death (1). For cases with undetermined chronicity of hyponatremia, the rate of correction has been recommended at not more than 10 mmol/L per first 24 h or 18 mmol/L for the next 48 h, and even slower rate of correction for patients at higher risk of ODS (1, 2, 3). However, despite correction of hyponatremia in accordance with guidelines, ODS can still occur (4, 5). We report a case of chronic hyponatremia secondary to severe anterior hypopituitarism in a patient with clinical

features of Noonan's syndrome. There was a complication of transient ODS which resolved due to quick actions taken to reduce further rise in sodium concentration.

Case presentation

A 50-year-old male presented to the emergency department with 2-day history of insomnia, severe nausea and dizziness. This was associated with a generalised dull headache. He denied any other neurological symptoms and weight loss. A thorough history taking revealed that he was diagnosed with 'hormonal deficiency' when he was 35 years old. He took oral hormonal replacement for 1–2 years and then defaulted follow up and treatment because he felt well. He was unable to recall the presenting

complaints that made him present to hospital, the details of his medications and tests performed then. These medical records were unavailable. At 42 years old, he presented to the hospital with abdominal pain and vomiting. A review of his old medical records revealed that his serum sodium concentration levels were significantly low at 101–105 mmol/L at that point. He received inpatient i.v. fluids and was initiated on hormonal replacement levothyroxine and hydrocortisone. MRI of the pituitary fossa showed a non-enhancing 2 mm lesion in the left pituitary gland with an impression of possibly a non-functioning micro-adenoma. He was discharged from inpatient stay against medical advice when he was asymptomatic, and sodium concentration was 105 mmol/L. A recheck sodium concentration outpatient 2 weeks later showed that it normalised at 135 mmol/L. He admittedly took the medications for a year only and again stopped because he was feeling well and was very poor. He defaulted the doctor's follow up and did not take hormonal replacements since then. He denied taking any regular medications, including diuretics or psychotropics. He did not have any repeat blood test since then. There was no available information about his growth and development in childhood. He came from a poor family with low socio-economic status.

Interestingly, despite having hypocortisolism and hypothyroidism, possibly for the last two decades, he was working full-time as a logistics assistant in an elementary school. His job scopes were simple repairs, cleaning and carrying things. His favourite pastime was playing simple computer games. He lived with a sibling who provided food and lodging for him. He did not smoke and did not drink alcohol. He never had any sexual interest, thoughts and did not remember his last erection or whether he had one before. He had a few friends and was a quiet person.

In the emergency department, he was afebrile, heart rate of 57 b.p.m., respiratory rate of 16 breaths per minutes and blood pressure of 119/58 mmHg and SpO₂ of 100% on room air. Despite an initial drip of 500 mL of normal saline prescribed by the emergency doctor, he was hypotensive the next morning with a blood pressure of 90/50 mmHg. Physical examination of the heart, lungs, abdomen and neurological system was unremarkable. However, he was noticeable for his smooth, young-looking facial skin, hairless face, absence of pubic and axillary hair and severe kyphoscoliosis of the thoracolumbar spine. Gynecomastia was present bilaterally, both testes were very small at less than 5 mL in volume each and his penile length was short at 5 cm. He did not have hypospadias. He had clinical features of Noonan syndrome which were short height (1.6 m), low set ears, a short neck, webbed neck, wide



Figure 1

The patient had features of Noonan syndrome and hypogonadism as shown in the pictures for (A) gynecomastia, (B) severe kyphoscoliosis, (C) widened cubital fossa and (D) webbed neck.

carrying angle of the elbows, and severe kyphoscoliosis (Fig. 1) (6). He did not have a cleft palate, hypotelorism or any facial signs of midline defect.

Investigation

This patient had hypo-osmolar hyponatremia with a serum sodium of 109 mmol/L, low serum osmolality of 229 mOsm/kg, urine sodium of 181 mmol/L and urine osmolality of 631 mOsm/kg. Endocrinological evaluation showed that he had anterior hypopituitarism, causing hypocortisolism, hypothyroidism, hypogonadism, and low growth hormone levels (Table 1). His free thyroxine T₄ and free T₃ levels were low at 6.45 and 2.03 pmol/L, respectively, with an inappropriately normal serum TSH of 4.28 mIU/L suggesting central hypothyroidism. During morning ward rounds by the primary team (i.e. day 2), blood test (08:00 h) was sent off immediately for serum cortisol which returned as very low at 86 nmol/L with an inappropriately normal serum ACTH of 35.5 ng/L



Table 1 Blood tests, hormonal results and urine tests of the patient.

Investigations	Patient	Reference range
Blood tests		
Sodium (mmol/L)	109	135–145
Osmolality (mOsm/kg)	229	275–300
Potassium (mmol/L)	4.0	3.5–5.3
Chloride (mmol/L)	77	96–108
Glucose (mmol/L)	4.7	3.1–7.8
Albumin (g/L)	50	37–51
25-Hydroxyvitamin D (µg/L)	19.3	30.0–100.0
Haemoglobin (g/dL)	12.0	13.0–17.0
White cells (×10 ³ /µL)	5.4	4.0–10.0
Serum hormones		
Free T4 (pmol/L)	6.45	10.00–20.00
Free T3 (pmol/L)	2.03	2.50–5.50
TSH (mIU/L)	4.28	0.400–4.00
Cortisol (08:00 h) (nmol/L)	86	170–500
ACTH (ng/L)	35.5	10.0–60.0
Testosterone (nmol/L)	<0.400	9.900–27.80
FSH (U/L)	0.40	1.00–12.00
LH (IU/L)	<0.50	0.57–12.07
SHBG (nmol/L)	114.1	15.0–50.0
Fasting 09:00 h GH (µg/L)	0.06	
IGF-1 (µg/L)	<25	48–209
Prolactin (mIU/L)	213.7	73.0–407.0
PTH (intact) (pmol/L)	2.84	1.30–7.60
Urine test		
Paired sodium (mmol/L)	181	40–220
Paired osmolality (mOsm/kg)	631	

TSH, thyroid stimulating hormone; ACTH, adrenocorticotropic hormone, FSH, follicle stimulating hormone; LH, luteinising hormone; SHBG, sex hormone binding globulin; GH, growth hormone; PTH, parathyroid hormone

indicating a central hypocortisolism state. The first dose of hydrocortisone was immediately given after the serum cortisol was taken but while awaiting the results, in view of the high clinical suspicion for hypocortisolism. He also had central hypogonadism as evidenced by a low serum total testosterone (<0.400 nmol/L), a low FSH (0.40 U/L), a low LH <0.50 IU/L. His serum IGF-1 was low (<25 µg/L). A repeat testing of fasting morning GH and IGF-1 levels at 3 months times showed persistently low and undetectable readings, suggesting growth hormone deficiency. Serum prolactin was normal at 213.7 mIU/L. He did not have central diabetes insipidus.

His spine X-ray showed marked kyphosis of the thoracic spine as well as lumbar scoliosis with convexity towards the left. There was no loss of vertebral height loss although his bone mineral density showed osteoporosis with *T* score –3.5 of the left femoral neck (0.472 g/cm²), *T* score of –3.2 of the left hip (0.592 g/cm²) and *T* score of –3.1 of the lumbar spine (0.641 g/cm²). His osteoporosis is likely caused by prolonged untreated

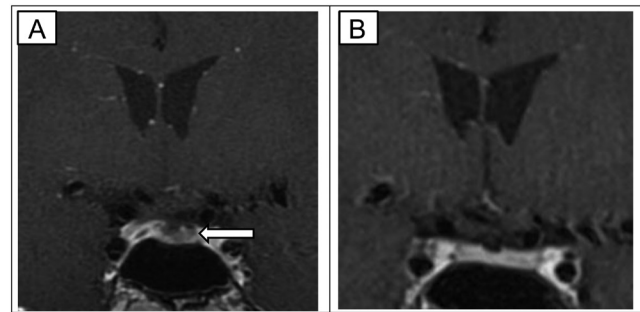
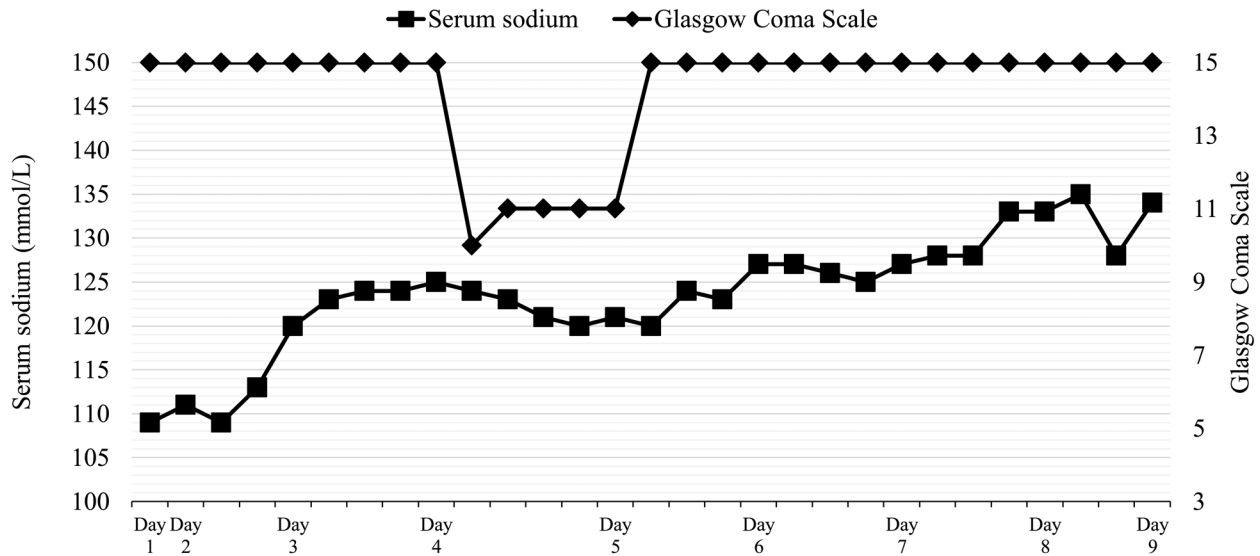


Figure 2 MRI pituitary scans with sequences using Coronal T1 weighted with contrast showed: (A) pituitary microadenoma of 8 mm (white arrow) 8 years ago and (B) normal pituitary.

hypogonadism and growth hormone deficiency. His ECG and echocardiogram tests were normal. He did not have any cardiac manifestations of Noonan syndrome, such as hypertrophic cardiomyopathy, pulmonary stenosis and atrial septal defects (6, 7). MRI pituitary revealed a normal pituitary and pituitary stalk (Fig. 2). The previously noted pituitary adenoma 8 years ago was no longer seen (Fig. 2). MRI brain performed was normal without any midline defect seen. These scans were performed inpatient after the patient had his seizure which is described subsequently.

Treatment

The acute management of his hyponatremia where he presented to at night to emergency department included i.v. normal saline (i.e. 0.9% NaCl) drip because he was symptomatic with dizziness, nausea and lethargy. By the next morning, that is within 12 h, the endocrine workup was performed, and his limited old medical records were reviewed by the inpatient medical team, leading to a diagnosis of chronic untreated anterior hypopituitarism, as well as a clinical diagnosis of Noonan syndrome. Caution was taken to increase his sodium level slowly yet surely, in order to improve his symptoms. Serum sodium was measured every 4–6 h. In the first 22 h of admission, he received 500 mL of 0.9% NaCl fluid and a single dose of i.v. 100 mg of hydrocortisone and his serum sodium increased by 4 mmol/L, from 109 to 113 mmol/L. In the subsequent 15 h, despite only receiving 150 mL of NaCl, his serum sodium level increased by 10 mmol/L, from 113 to 123 mmol/L (Fig. 3). Because his vitals were stable and symptoms improved, after the single dose of i.v. hydrocortisone, this was changed to oral hydrocortisone. A low dose of levothyroxine was started the following day and titrated upwards gradually. The aim now was to avoid further rapid rise of his serum sodium level, and his



IV fluids	500 ml NS	150ml Normal Saline(NS)	1000ml 5% dextrose	1000ml 5% dextrose	500ml 5% dextrose	1000ml 5% dextrose per day				
Hydrocortisone (route, dose)	-	IV 100mg PO 20mg	PO 20mg	PO 10mg	IV 25mg PO 5mg	PO 20mg x 2 doses per day				
Thyroxine (route, dose)	-	-	PO 50mcg	-	PO 50mcg	PO 50mcg per day				
Desmopressin (route, dose)	-	-	-	IV 1mcg	-	IV 1mcg	-	-	-	-

Figure 3

The trend of serum sodium concentration and Glasgow Coma Scale of the patient during his hospital stay. Various fluids and medications given at specific time points are illustrated. PO, peroral.

sodium level was maintained at 123–125 mmol/L in the next 24 h (days 3–4 of admission).

However, despite these efforts, he developed an acute episode of hypertonia and aphasia (GCS level E4V1M5) on day 4 when his serum sodium level was 124 mmol/L. On examination, he was alert, eyes open but unable to speak, with significantly increased tone in upper limbs and drooling evident. MRI of the brain performed within the next 2 h was normal. He also had an episode of partial seizure with witnessed repetitive movements of his right arm, lasting for approximately 3 min, which terminated spontaneously. He was prescribed antiepileptic agent sodium valproate to prevent further seizures. To reduce his serum sodium level, i.v. 1 µg of desmopressin and i.v. dextrose 5% fluids were given. His serum sodium level was successfully reduced to 120–122 mmol/L over the next few hours, with complete neurological recovery the next day (day 5 of admission). His serum sodium level was closely monitored with the aim of a rise of not more than 5 mmol/L/day until normalisation of his serum sodium level to 135 mmol/L (Fig. 3). Another repeat MRI of the brain (day 5 of admission) was again normal and

did not show signs of osmotic demyelination. Although, radiological signs of demyelinating lesions can be delayed at about 5 days after ODS (8), no further MRI scans were performed as he had completely recovered.

Outcome and follow-up

This patient was reviewed in the endocrinology outpatient clinic at 1, 3 and 6 months after hospital discharge. He was alert, jovial and talkative, unlike his previous self. His serum sodium and serum-free T4 levels were normal. He was also commenced on testosterone replacement therapy. The chronic management of this patient included education of adherence of hormonal replacement hydrocortisone and levothyroxine. Advice to increase hydrocortisone dose on sick days was frequently emphasised to him and his family. With the help of our medical social worker, the patient did not have to worry about financial payment for his medical treatment and he was able to obtain appropriate medical care through government's subsidy. This helped to prevent further default of medical follow up.



Discussion

We reported a case of Noonan syndrome, that presented with chronic severe hyponatremia secondary to severe anterior hypopituitarism. This case has a few interesting points. This patient survived and worked many years with severe hyponatremia, hypocortisolism and hypogonadism despite presenting with a few admissions for symptomatic severe hyponatremia. He never suffered from hypocortisolic crisis, myxedema coma or cerebral oedema before. This case report showed that quick action to lower sodium level could avoid permanent ODS sequelae. This case report also adds to the rarely described cases of patients with Noonan syndrome and hypopituitarism in the literature (9, 10).

Usually, patients with Noonan syndrome present with growth issues including short stature and delayed puberty (7). This is likely to be related to genetic defects in the RAS-MAPK (mitogen-activated protein kinase) pathway (7). Mutations of *PTPN11*, *SOS1*, *RAF1*, *MEK1* and *RAS* have been detected in Noonan Syndrome with *PTPN11* mutations being the most common (7). While these mutations have not been directly associated with hypopituitarism, *PTPN11* protein product SHP-2 (Src homology region 2-domain phosphatase 2) is a cytoplasmic protein with tyrosine phosphatase actions which is important in the signalling pathway of growth factors, IGF-1, insulin, leptin and cytokines (7). Therefore, mutation such as of *PTPN11* or yet-to-be identified mutations could account for the concomitant hypopituitarism in this patient, however, this is speculative as genetic testing was not performed in this case.

Chronic hypocortisolism, severe hyponatremia and chronic hyponatremia increased his risk of having ODS. Low levels of cortisol fail to suppress vasopressin, resulting in impaired excretion of free water (3). When cortisol level is replaced, this leads to inhibition of vasopressin and increases the free water excretion leading to sodium concentration rising. Neurological impairments due to ODS are caused by brain dehydration leading to shrinkage of brain cells. In our case, although the rise of serum sodium concentration was only 14 mmol/L over 48 h, the abrupt rise during days 2–3 from the water diuresis from hydrocortisone replacement as well as the use of a small amount of NaCl precipitated the episode of ODS. Other risk factors associated with a higher risk of developing ODS are alcohol abuse, liver disease, use of thiazides and/or antidepressants (3). Poor insight and understanding of the importance of hormone replacement adherence can lead to devastating consequences. Hypopituitarism,

in particular, glucocorticoid deficiency is an important cause of hyponatremia and hypocortisolism crisis (1, 2, 3). Patient education, especially in conditions of chronic hormonal deficiencies is key in ensuring patients remain adherent to treatment.

ODS is commonly observed in patients with chronic severe hyponatremia that has been corrected by >10–12 mmol/L per day or >18 mmol/L in 48 h (11). However, ODS was also reported in patients whose chronic hyponatraemia was corrected at a recommended rate (4, 5). To avoid ODS, correction of chronic hyponatremia at a rate of <12 mmol/L/day was recommended as early as 1986 (12). Subsequently, experts suggest that a correction rate of 4–6 mmol/L/day is sufficient for both acute and chronic hyponatremia (11). However, the optimal rate of correction is controversial. A systematic review revealed a total of eight guidelines that recommended varying rates of correction between 8 and 12 mmol/L per day, as well as different doses of normal saline and infusion speed (2). In cases of severe symptomatic hyponatremia, under-correction of serum sodium levels leads to morbidity and hypertonic saline would generally be first-line treatment (2). As seen in our case, it is judicious to correct serum sodium slowly, especially when given hydrocortisone replacement, which can increase the serum sodium levels much more than intended or expected (11). Although hydrocortisone itself without i.v. normal saline may be sufficient to improve hyponatremia in a hypocortisolic patient who is drinking orally, this patient was necessarily prescribed the i.v. normal saline in view of his symptoms of dizziness, nausea, and hypotension in the ward. The management can be challenging as the extent of sodium-raising effect of hydrocortisone is not quite predictable.

Desmopressin has been shown to reduce the rate of serum sodium correction from 0.81 to –0.02 mmol/L/h, and reduce the magnitude of variation of serum sodium levels (13). While a systematic review showed that while proactive approach with desmopressin was shown to be associated with a lower incidence of overcorrection of serum sodium (14), reactive approach has also been favoured by others (15), and thus, it remains undetermined when desmopressin should optimally be given (9, 10). Although the prognosis of ODS is better than previously thought with about half of the patients having favourable outcomes, the same study showed that about 30% of patients admitted to intensive care died at 1-year follow-up. This highlights the importance of avoiding ODS (16). The management of chronic hyponatremia should be individualised depending on the clinical picture and circumstances.



Patient's perspective

I felt more energetic and alert after several months of hormonal replacement. I am working full-time, as well. My family and friends have also noted the improved difference in me. They said that I am more energetic, cheerful, and active than previously.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from the patient for publication of this article and the accompanying images.

Author contribution statement

W J L was the primary physician of the patient. T H C and W J L managed the patient, wrote the manuscript and approved the final version of the manuscript.

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