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Primary polydipsia in a family with a known mutation in the AVP gene

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Background

- Diabetes insipidus (DI) is characterised by inappropriate production of large volumes of dilute urine even in the presence of clinical dehydration or deprivation of water. It is due to deficiency or insufficiency of arginine vasopressin (AVP) hormone production, known as central DI, or because of renal unresponsiveness, nephrogenic DI.
- The water deprivation test is the gold standard diagnostic test.
- Hereditary DI accounts for < 10% of the DI cases seen in clinical practice[1]. Two forms of hereditary DI exist, familial neurohypophyseal (central) DI (FNDI) and congenital nephrogenic DI.
- FNDI is inherited in an autosomal dominant pattern and to date 69 different mutations in the AVP gene causing FNDI have been described[2].
- Cases of primary polydipsia (habitual water drinking) can co-exist in families where central DI has been diagnosed, especially where there is a different perception of what is normal fluid intake. On the other hand, primary polydipsia does not exclude the patient from developing DI in the future and genetic testing in family cases may therefore be indicated. Determining the presence of a mutation in the AVP gene in cases of familial central diabetes insipidus (DI) is useful particularly in individual patients who are not yet symptomatic or are only partially symptomatic and repeatedly pass the water deprivation test or who give inconclusive results.
- We present a family which illustrates issues which may occur in FNDI.

Cases

A family with a known heterozygous pathogenic missense mutation, c. 232>A (GLU78LYS) in AVP gene affecting a mother and 2 of 4 children.

Case 1: Mother presented aged 22 to the adult endocrinology service with a 5 year history of polydipsia and polyuria. She was drinking up to six litres of water a day and was micturating ten times during the day and up to five times at night. A water deprivation test confirmed the clinical diagnosis of central DI. (See Table 1).
MRI of the pituitary showed no abnormality.

Further history revealed that her own mother had symptoms of polydipsia and polyuria since her early twenties and a maternal aunt had symptoms of polydipsia since childhood. Neither the patient's aunt nor mother had a formal diagnosis and both are now deceased.

Case 2: Presented to the Paediatric clinic at age 3 years. A water deprivation test was normal but her mother was convinced that she was exhibiting symptoms of polyruria and polydipsia, and water seeking behaviour, as she had suffered prior to her own diagnosis. A trial of desmopressin was instituted which resulted in dramatic symptomatic and behavioural improvement. She is now thirteen years old and maintained on a dose of 20mcg of desmopressin twice daily. Weight and height are on the 75th centile. A water deprivation test recently confirmed the clinical diagnosis of DI (Table 2).

Case3: Presented at age 7 years with symptoms of polyuria, polydipsia and water seeking behaviour. A trial of desmopressin had not resulted in symptomatic or behavioural improvement. Three water deprivation tests were conducted in 2011, and 2013 (Table 3) which were all normal demonstrating good concentrating ability of the kidneys. Due to persistent symptoms and her strong family history of central DI, genetic analysis of the AVP was sent to aid with future management and was found to be positive for the same pathological missense mutation. An older brother with a history of transient polydipsia at age 2 had a normal water deprivation test - genetic results are negative.

Table 1

Time (hours)	Serum osmo mOsmo/kg	Urine osmo mOsmo/kg	Na (mmols/l)	Weight (kg)
6:00am	282	61	137	61.2
9:00	288	140	139	60.2
11:00	292	180	142	59.6
12.00	301	355	144	59.5
DDAVP given				
15:00	292	550	142	59.4

Table 2

Time (hours)	Serum osmo mOsmo/kg	Urine osmo mOsmo/kg	Na (mmols/l)	Weight (kg)
6:00am	294	816	139	53.2
9:00	295	107	141	50.2
11:00	298	98	142	50.2
12:00	301	161	145	50.0
DDAVP given				
15:00	293	N/A	142	50.8

Table 3

Time (hours)	Serum osmo mOsmo/kg	Urine osmo mOsmo/kg	Na (mmols/l)	Weight (kg)
8.00am	293	664	141	53.2
10:00	292	728	141	50.2
12:00	292	794	140	50.2
14.00	294	862	136	50.0

MRI Images

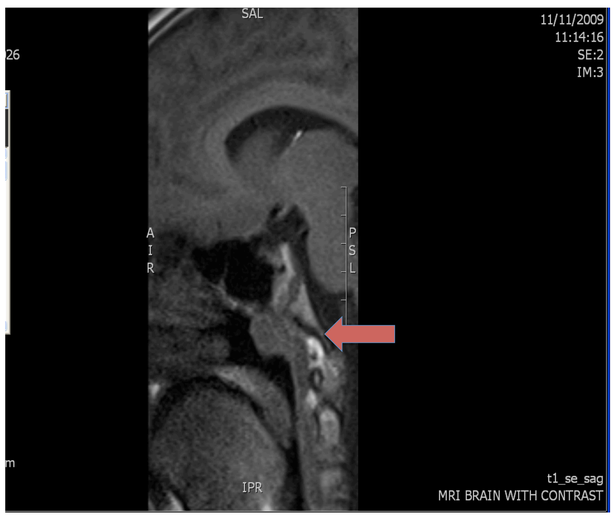

Figure 1: Saggital view of the pituitary gland of case 1, showing absence of posterior pituitary bright spot.

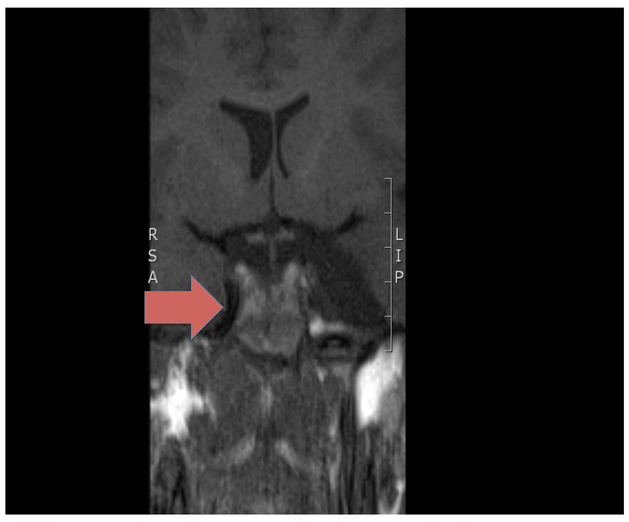

Figure2: Coronal view of the pitutary gland of case 2, also demonstrating an absent posterior pituitary bright spot

Discussion

This case highlights the value of a thorough family history as a stepping stone to the discovery of an inherited disorder. The diagnosis of familial DI is important as water deprivation tests can be difficult to perform particularly in the paediatric population. The presence of a known genetic mutation in one family member should prompt testing of first degree relatives as this inherited disorder is associated with significant distress for patients but is very easily managed with daily dosing of desmopressin. This case also highlights that both psychogenic polydipsia and DI can co-exist within families and indeed psychogenic polydipsia pre dated the diagnosis of DI in Case 2, reminding us of the importance of on going surveillance and serial testing as inappropriate treatment can be dangerous in extreme cases leading to hyponatraemic seizures.

References

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