CASE REPORT

'If there were water we should stop and drink': neurofibromatosis presenting with diabetes insipidus

Rachel Barry,¹ Antoinette O' Connor,¹ Mohn Hazriq Awang,² Orna O' Toole¹

¹Department of Neurology, Mercy University Hospital, Cork, Ireland

²Department of Endocrinology, Mercy University Hospital, Cork, Ireland

Correspondence to

Dr Rachel Barry, rachelbarry91@gmail.com

RB and AO'C contributed equally.

Accepted 22 January 2018

SUMMARY

A 58-year-old right-handed woman presented to our institution with a 1-month history of polydipsia and polyuria. She had a remote history of neurofibroma excision by dermatology and, on examination, was noted to meet the clinical diagnostic criteria for neurofibromatosis type 1. Laboratory investigations revealed hypernatraemia and elevated serum osmolality, accompanied by reduced urinary osmolality. A subsequent water deprivation test confirmed central diabetes insipidus, which responded to treatment with desmopressin. MRI of the brain showed pituitary enlargement, which raised the possibility of an underlying pituitary adenoma or, alternatively, lymphocytic hypophysitis. Both conditions have rarely been described in neurofibromatosis.

BACKGROUND

Neurofibromatosis type 1 (NF1) is a reasonably common genetic condition¹ associated with characteristic skin changes, and an increased frequency of benign, and malignant, tumours of the nervous system. We report a case of NF1 that presented with polyuria and polydipsia secondary to central diabetes insipidus.

CASE PRESENTATION

A 58-year-old right-handed woman presented to our institution with a 1-month history of nausea, polydipsia and polyuria. She reported drinking approximately 5–6 L of water per day and was passing urine at least three times per night. Her weight was stable, and she had not experienced any recent head injury. Her only medication was

metoclopramide (as required), which was first prescribed 3 weeks before her presentation. She had never been treated with lithium. Her medical history was significant for a cutaneous neurofibroma excised 12 years previously. She had never been seen by a neurologist. There was no family history of neurofibromatosis. On examination, she was found to have multiple neurofibromas, four café au lait spots, Lisch nodules and freckling of her left axilla. Her neurological examination, including visual fields, was normal.

INVESTIGATIONS

Laboratory investigations on admission (table 1) revealed hypernatraemia (sodium: 150 mmol/L) and elevated serum osmolality (302 mOsm/kg), accompanied by reduced urinary osmolality (82 mOsm/kg). Serum glucose was normal (5.6 mmol/L). Creatinine, serum ACE, thyroid and liver function tests were normal. CT of the brain was normal, aside from multiple cutaneous neurofibromas (figure 1). MRI of the brain (figures 2 and 3) showed global asymmetric enlargement of the pituitary gland, including stalk, 1.8 cm coronally, 0.8 cm vertically, 1.1 cm anteroposteriorly, with suprasellar extension posteriorly. There was heterogeneous enhancement of the gland on the postcontrast images, with smooth uniform enhancement of the pituitary stalk. The posterior pituitary bright spot was retained. A water deprivation test (table 2) was performed. The absence of antidiuretic hormone, in the setting of elevated serum osmolality, was suggestive of central diabetes insipidus. The diagnosis was confirmed when subsequent testing revealed a >50% rise in urine osmolality in response to desmopressin. Additional investigations (table 2) were performed to rule out another endocrinopathy.

TREATMENT

Serum sodium normalised following the introduction of desmopressin.

OUTCOME AND FOLLOW-UP

Our patient improved both clinically and biochemically following treatment with desmopressin.

She was discharged home 1 week after her initial presentation. During her admission, she was formally given a diagnosis of NF1, as two of the seven clinical criteria were satisfied (table 1). Neuroradiology and neurosurgery services reviewed her MRI. Surveillance imaging was recommended, as it was unclear whether pituitary swelling represented a pituitary

Table 1 Blood tests

Test	Result	Reference range
TSH	1.85	0.35–4.9 mIU/L
Prolactin	1015 ↑	109–577 mIU/L
IGF-1	148	46–238 ng/mL
FSH	38	26.7–133.4 IU/L
LH	20.3	5.2–62 mIU/L
ACTH	3.1	1.1–13.2 pmol/L
Cortisol (morning)	345	171–800 nmol/L
K ⁺	3.5	3.5–5.5 mmol/L
Ca ²⁺ (corrected)	2.4	2.1–2.55 mmol/L

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; IGF-1, insulin growth factor-1; LH, luteinising hormone; TSH, thyroid-stimulating hormone.

To cite: Barry R, O' Connor A, Awang MH, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222741

Figure 1 CT of the brain demonstrating cutaneous neurofibromas. Nil pituitary abnormality identified.

adenoma or lymphocytic hypophysitis. She continues to attend neurology and endocrinology clinics.

DISCUSSION

NF1 was first described by Frederick von Recklinghausen in 1882.¹ It is an autosomal dominant condition with a prevalence of 1 in 2500 to 3000 people worldwide.¹ A germline mutation in the NF1 tumour suppressor gene on chromosome 17 results in typical skin changes and an increased frequency of benign and malignant tumours, particularly of the nervous system.

Figure 2 MRI of the brain: sagittal view showing global pituitary enlargement.

Figure 3 MRI of the brain: coronal view showing global pituitary enlargement.

Associated tumours include glioma of the optic nerve pathway, glioblastoma, malignant peripheral nerve sheath tumour, gastrointestinal stromal tumour, breast cancer, pheochromocytoma, duodenal carcinoid tumour and rhabdomyosarcoma. Fifty per cent of individuals with NF1 have no family history of the disease, as in our patient.¹ These cases are attributed to de novo mutations. The diagnosis of NF1 is a clinical one, using established criteria (box 1). NF1 gene testing is reserved for unusual presentations or to inform reproductive decision-making.²

Pituitary abnormalities, including both pituitary adenoma and lymphocytic hypophysitis, have been rarely described in patients with NF1, although recognition is increasing.³ Attention to the suprasellar region, in addition to the brain tissue, and orbits, on brain imaging of patients with NF1 is advised. The presence of pituitary swelling in our patient adds to the evidence that the suprasellar fossa should be carefully reviewed when performing intracranial imaging of an NF1 carrier.

No single radiological feature distinguishes pituitary adenoma from lymphocytic hypophysitis so patients must have functional endocrine testing, imaging and be followed clinically if histology is not available. An asymmetrical, heterogeneously enhancing lesion with maintained posterior pituitary bright spot supports pituitary adenoma; while stalk involvement and volume $<6\text{ cm}^3$ would favour lymphocytic hypophysitis.⁴

One previous case of neurofibromatosis with lymphocytic hypophysitis, an autoimmune inflammation of pituitary tissue, has been reported.⁵ Presentation is typically with headache, hypopituitarism and central diabetes insipidus (CDI). In NF1, overexpression of the neurofibromin gene leads to suppression

Table 2 Water deprivation test

Test	Result	Reference range
Antidiuretic hormone	$<0.5\downarrow$	4–14 ng/L
Serum osmolality	297	275–295 mOsm/kg
Urine osmolality	Pretest: $65\downarrow$ Post-test: 236 ($>50\%$ rise)	300–900 mOsm/kg

Box 1 Clinical criteria for diagnosis of neurofibromatosis type 1 (NF1)

- ▶ ≥6 Café au lait macules >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals.
- ▶ ≥2 Neurofibromas of any type or >1 plexiform neurofibroma.
- ▶ Freckling in the axillary or inguinal regions.
- ▶ Optic glioma.
- ▶ ≥2 Lisch nodules (iris hamartomas).
- ▶ A distinctive osseous lesion, such as sphenoid dysplasia or thinning of the long bone cortex, with or without pseudoarthrosis.
- ▶ A first-degree relative (parent, sibling or offspring) with NF1 according to the above criteria.

of Fas ligand, and subsequent lack of apoptosis of CD4 +T lymphocytes. This leads to an increased incidence of other autoimmune conditions including vitiligo, Hashimoto's thyroiditis and Graves disease in patients with NF1.^{6,7} Our patient did not have headache or hypopituitarism on the testing performed and improved without immunotherapy. This case suggests that lymphocytic hypophysitis may be an additional autoimmune complication that can occur in NF1.

Diabetes insipidus is a rare complication of NF1. Only two cases have been previously reported. One of these patients also suffered from myelodysplastic syndrome secondary to monosomy 7, a condition that has also subsequently been linked to CDI.^{8–10} CDI is a pathological deficiency in the secretion of antidiuretic hormone (ADH), resulting in failure to maintain optimal plasma osmolality.¹¹ Increased plasma osmolality above 280 mOsmol/kg is detected by osmoreceptors of the anterior hypothalamus, triggering ADH release into the circulation.¹¹ ADH acts on V2 receptors in the nephron, leading to reabsorption of free water.¹¹ ADH deficiency presents clinically with polyuria and polydipsia. It can be diagnosed by demonstrating low levels of antidiuretic hormone in the setting of elevated serum osmolality. Although plasma ADH levels can be measured,

caution should be applied when interpreting the results of ADH immunoassays, as levels may be artefactually low due to instability ex vivo. In this case, we confirmed CDI by demonstrating a greater than 50% increase in urine osmolality postdesmopressin. Our case illustrates CDI in a patient with NF1 with polyuria, hypernatraemia and an enlarged pituitary. Patients with NF1 may be at increased risk of CDI due to a genetic increased risk of both tumours and deranged T lymphocyte function, within the nervous system.

Acknowledgements We acknowledge Dr Matthew Murphy, Consultant Endocrinologist, Mercy University Hospital who provided expert endocrinology opinion and provided follow-up in specialist endocrinology outpatient clinic.

Contributors RB (neurology Senior House Officer) involved in following the patient during her initial presentation; arranging and interpreting of investigations; write-up of case report. AO'C (neurology Specialist Registrar) involved in following the patient during her initial presentation; arranging and interpreting of investigations; write-up of case report. MHA (endocrinology registrar) involved in following the patient during her initial presentation; arranging and interpreting of investigations; arranging patient consent. OO'T (neurology Consultant) consulted on the patient during her initial presentation for expert neurological opinion; provided diagnostic advice; proof-reading of case write-up; provided follow-up for the patient in neurology outpatient clinic.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. *Lancet Neurol* 2014;13:834–43.
- 2 Gutmann DH, Aylsworth A, Carey JC, *et al.* The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA* 1997;278:51–7.
- 3 Caimari F, Korbonsits M. Novel Genetic Causes of Pituitary Adenomas. *Clin Cancer Res* 2016;22:5030–42.
- 4 Gutenberg A, Larsen J, Lupi I, *et al.* A radiologic score to distinguish autoimmune hypophysitis from nonsecreting pituitary adenoma preoperatively. *AJNR Am J Neuroradiol* 2009;30:1766–72.
- 5 Idiculla J, Pakalomattom S, Desai A, *et al.* Neurofibromatosis type 1 and lymphocytic hypophysitis: Single trigger and double shots? *Int J Rheumatology and Clin Immunology* 2015;3:CS3.
- 6 Bolko P, Wasko R, Waligórska J, *et al.* [Graves' disease and hyperprolactinemia in a patient with Noonan syndrome neurofibromatosis type 1]. *Ann Endocrinol* 2004;65:121–4.
- 7 Yalcin B, Yalcin B, Tamer E, *et al.* Neurofibromatosis 1/Noonan syndrome associated with Hashimoto's thyroiditis and vitiligo. *Acta Derm Venereol* 2006;86:80–1.
- 8 Surapolchai P, Ha SY, Chan GC, *et al.* Central diabetes insipidus: an unusual complication in a child with juvenile myelomonocytic leukemia and monosomy 7. *J Pediatr Hematol Oncol* 2013;35:e84–7.
- 9 Kollen WJ, Ball LM, Snijder P, *et al.* Diabetes insipidus in a child with a monosomy-7 associated myelodysplastic syndrome and neurofibromatosis I. *Med Pediatr Oncol* 2003;40:257–9.
- 10 Geoffroy H, Zniher A, Kouhen C, *et al.* [Recklinghausen's neurofibromatosis, diabetes insipidus and xanthomatosis]. *Maroc Med* 1963;42:611–3.
- 11 Wijetilleka S, Khan M, Mon A, *et al.* Cranial diabetes insipidus with pituitary stalk lesions. *QJM* 2016;109:703–8.

Learning points

- ▶ Neurofibromatosis type 1 (NF1) is a condition that is diagnosed on clinical examination. Although there is genetic linkage, a family history is not mandatory.
- ▶ Patients with NF1 are at increased risk of developing both benign and malignant tumours, among which pituitary adenoma should be considered.
- ▶ NF1 carriers are at increased risk of autoimmune conditions.
- ▶ Central diabetes insipidus is a rare complication of NF1.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow