

## CASE REPORT

# Neurofibromatosis 1-associated panhypopituitarism presenting as hypoglycaemic seizures and stroke-like symptoms

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Accepted 15 October 2015

## SUMMARY

A 37-year-old man with a known history of neurofibromatosis 1 (NF1) presented within 2 days of diarrhoeal illness followed by encephalopathy, facial twitching, hypoglycaemia, hypotension, tachycardia and low-grade fever. Examination showed multiple *café-au-lait* spots and neurofibromas over the trunk, arms and legs and receptive aphasia with right homonymous hemianopia, which resolved. Workup for cardiac, inflammatory and infectious aetiologies was unrevealing. A brain MRI showed gyral swelling with increased T2 fluid-attenuated inversion recovery signal and diffusion restriction in the left cerebral cortex. Neuroendocrine findings suggested panhypopituitarism with centrally derived adrenal insufficiency. Supportive treatment, hormone supplementation, antibiotics, antivirals and levetiracetam yielded clinical improvement. A follow-up brain MRI showed focal left parieto-occipital atrophy with findings of cortical laminar necrosis. In conclusion, we describe a case of NF1-associated panhypopituitarism presenting as hypoglycaemic seizures and stroke-like findings, hitherto unreported manifestations of NF1. Prompt recognition and treatment of these associated conditions can prevent devastating complications.

## BACKGROUND

Neurofibromatosis 1 (NF1) is one of the most common inherited autosomal dominant neurological disorders, affecting about 1 in every 3000 individuals, with established diagnostic criteria.<sup>1</sup> NF1 is a multisystem disorder with several neurological and non-neurological manifestations;<sup>2</sup> however, involvement of the pituitary—hypothalamic axis is rarely reported.<sup>3–5</sup> While some reports identified structural causes, such as pituitary adenoma and hydrocephalus,<sup>3–4</sup> others describing short stature related to growth hormone (GH) deficiency noted the absence of sellar or suprasellar pathology on neuroimaging.<sup>5</sup> There is limited published literature on hypoglycaemic seizures and stroke-like symptoms related to NF1-associated panhypopituitarism. We describe a case of NF1-associated panhypopituitarism presenting as hypoglycaemic seizures and stroke-like symptoms and features indicating an adrenal crisis-like presentation; further, our case manifested several other rare systemic complications of NF1.

## CASE PRESENTATION

A 35-year-old man with known NF1, learning disability and a history of NF1 in his father presented to an outside hospital with diarrhoea and dehydration, which improved with intravenous fluids. Two days later, his roommate found him confused and minimally responsive with facial twitching. Initial evaluation showed sinus tachycardia, systolic blood pressure ranging from 70 to 100 mm Hg, temperature 99.5°F and a Glasgow Coma Scale score of 8 (withdrawal to pain, non-verbal, opening eyes to commands). Rapid intravenous administration of 25 g dextrose, to correct a blood glucose level of 32 mg/dL, produced no change in mental status and prompted emergent intubation for airway protection. There had been no prior reported episodes of hypotension, hypoglycaemia or altered responsiveness.

## INVESTIGATIONS

### Initial testing

Laboratory studies revealed polymorphonuclear leucocytosis, mild normocytic normochromic anaemia (haemoglobin 11.2 g/dL and haematocrit 33.1%), metabolic acidosis with an anion gap of 25, acute kidney injury with a newly elevated creatinine of 1.5 mg/dL and a mild troponin elevation (1.42 ng/mL; normal <0.05), but no ischaemic ST or T-wave ECG changes. Urine toxicology screen, liver function tests, electrolytes, lactic acid level and erythrocyte sedimentation rate (ESR) were normal. Chest X-ray showed left lower lobe opacity suggestive of an infiltrate or effusion; serial follow-up studies suggested basilar atelectasis.

The initial clinical impression was of a patient with encephalopathy with possible seizures, in the setting of low-grade fever, hypotension, hypoglycaemia and mild metabolic derangements. Diagnostic testing was undertaken to address the following identified pathologic disorders.

### Seizures and obtunded mental status

Lumbar puncture performed after a normal CT of the brain yielded traumatic cerebrospinal fluid (CSF) with an opening pressure of 32 cm H<sub>2</sub>O, >10 000 red blood cell/mm<sup>3</sup> in tubes 1 and 3, 346 white cell count/mm<sup>3</sup> in tube 3 (91% polymorphs), glucose 43 mg/dL (serum glucose 74 mg/dL obtained after 25 g intravenous dextrose) and total protein 370 mg/dL (normal 15–60). Gram's stain, bacterial culture, Lyme antibody titre, herpes



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**To cite:** Waheed W, Nathan MH, Allen GB, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-210816

simplex virus PCR, venereal disease research laboratory, cryptococcal antigen and cytology were normal or negative.

The MRI of the brain showed gyral swelling, increased T2 fluid-attenuated inversion recovery signal and diffusion restriction in the left frontal, parietal and occipital cortices (figure 1). The CT angiogram, as well as subsequent conventional angiography, of the head and neck was normal. Electroencephalogram showed delta activity over the left parieto-occipital and temporal regions without interictal epileptiform discharges.

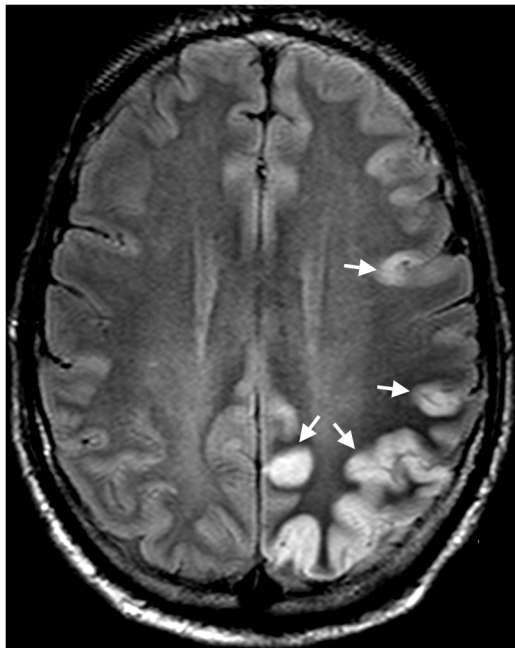
Vasculitis related and cardioembolic causes were excluded by autoimmune panel testing (ESR, antinuclear antibodies, antineutrophil cytoplasmic antibody and rheumatoid factor) and echocardiography.

#### Hypotension and suspected sepsis

Search for a source of sepsis with cultures of blood, urine, CSF and stools, and serum viral antibody panels was negative. CT of the abdomen and pelvis, done for evaluation of diarrhoea, anaemia and hypotension, showed no fluid collection or free air, but revealed enhancement of a large portion of the small bowel and most of the colon suggestive of hypoperfusion complex (shock bowel), which improved with appropriate fluid management. Additionally, the CT of the pelvis showed a moderate-sized left hip effusion; arthrocentesis yielded normal joint fluid.

#### Hypoglycaemia

A CORTROSYN™ (cosyntropin) stimulation test with 250 µg of synthetic adrenocorticotrophic hormone (ACTH), performed to investigate hypoglycaemia and shock on the day of hospitalisation, demonstrated baseline, 30 and 60 min post-stimulation cortisol levels of <1.0 µg/dL. A full thyroid profile performed



**Figure 1** MRI of the brain—axial T2 fluid-attenuated inversion recovery sequence just above the lateral ventricles showing areas of gyral swelling and increased signal intensity (white arrows) limited to the cortex in the left middle cerebral, posterior cerebral and distal anterior (precuneus) cerebral artery territories. These areas were matched for abnormalities in diffusion-weighted images and the apparent diffusion coefficient map (not shown).

on the day of presentation, and subsequent pituitary-related testing obtained approximately 2 weeks after the presentation, confirmed findings of panhypopituitarism (table 1). The normal prolactin level was probably related to seizures prior to testing; the follicle-stimulating hormone level was not obtained. On the basis of the results of the static neuroendocrine test battery, a subsequent MRI of the brain obtained with dedicated pituitary views showed no abnormality (figure 2).

#### TREATMENT

The patient was treated with intravenous fluids, broad-spectrum antibiotics and antiviral drugs for possible sepsis and/or meningoencephalitis (ceftriaxone 2 g q12 h for 2 days, vancomycin 1 g q12 h for 6 days, ampicillin 2 g q4 h for 1 day, ciprofloxacin 400 mg intravenous q12 h for 5 days and acyclovir 5 mg/kg q8 h for 1 day), and levetiracetam for facial twitching concerning seizures. Hormone replacement therapy was provided with hydrocortisone, followed later by thyroid hormone and testosterone therapy.

#### OUTCOME AND FOLLOW-UP

The patient improved quickly, with resolution of cardiac, renal and metabolic abnormalities. After extubation, over the next week, antibiotic and antiviral drugs were discontinued. Since the possible seizures were deemed to be provoked by hypoglycaemia and metabolic abnormalities, levetiracetam was discontinued approximately 1 month later.

Post-extubation, a focused skin examination showed multiple *café-au-lait* spots and neurofibromas on the trunk, arms and legs. Neurological examination revealed a mild receptive aphasia and partial right homonymous hemianopia, both of which improved during rehabilitation over the ensuing few months.

Further evaluation of left hip pain with an MRI showed several intra-articular and extra-articular plexiform neurofibromas (figure 3) and a meningocele in the sacral spinal canal (figures 4).

A follow-up MRI of the brain obtained 6 months following discharge (figure 5A, B) showed abnormalities in the left parieto-occipital region compatible with the sequelae of cortical laminar necrosis, with injury/atrophy of the underlying white matter, and post-injury atrophy and signal abnormality in the splenium of the corpus callosum.

An additional review of the patient's previous medical records, which were subsequently made available, revealed two separate remote episodes of spontaneous pneumothorax (figures 6 and 7), believed to be related to extensive blebs and bullae seen in both lungs on CT imaging, most notably in the upper

**Table 1** Endocrine testing

Test	Patient result	Normal range
Adrenocorticotrophic hormone levels	<10 pg/mL	10–60
Insulin-like growth factor	77 ng/mL	113–297
TSH	7.02 µU/mL	0.35–5.00
T3	58 ng/dL	60–181
Free T4	0.7 ng/dL	0.8–1.8
Testosterone	192 ng/dL	241–827
Free testosterone	2.6 ng/dL	5.0–24.0
Luteinising hormone	2.8 mIU/mL	2–9
Prolactin	11.2 ng/mL	2.1–17.1

TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine.



**Figure 2** MRI of the brain—sagittal T1-weighted image through the mid-sagittal plane showing a normal pituitary gland (white arrow).

lobes. These pulmonary findings were felt to be in keeping with the diagnosis of NF1-related lung disease.

#### DISCUSSION

The diagnosis of NF1 in our case was primarily based on the presence of multiple *café-au-lait* spots, neurofibromas (including 1 plexiform neurofibroma) and a first-degree relative with NF1.



**Figure 3** MRI of the left hip—coronal post-contrast fat-suppressed T1-weighted image showing the plexiform neurofibroma with both intracapsular (black asterisk) and extracapsular components (double white arrows) (biopsy proven). The single white arrow indicating an extracapsular component eroding the bone in the lateral supra-acetabular region.



**Figure 4** MRI of the lumbosacral spine—sagittal T2-weighted MRI demonstrating dural ectasia (black asterisk) of the sacral thecal sac remodelling and expanding the surrounding bone of the spinal canal (white arrows). The black arrows indicating the nerve roots normally dispersed within the sacral thecal sac.

Additional features that supported the diagnosis included: (1) central nervous system (CNS) manifestations of panhypopituitarism, seizures and learning disability; (2) peripheral nervous system manifestations of plexiform neurofibromas in the hip and sacral spinal canal meningocele and (3) systemic manifestations of recurrent spontaneous pneumothorax.

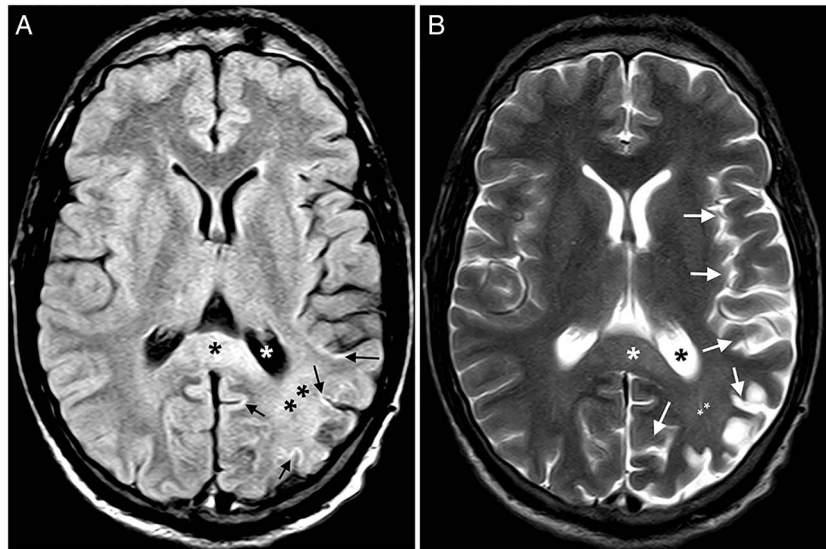
NF-1 is an autosomal dominant disorder caused by a mutation in the gene encoding neurofibromin, located on chromosome 17q11.2. Neurofibromin is a multifunctional tumour suppressor protein involved in the regulation of many cellular pathways related to cell growth and proliferation.<sup>6</sup> Neurofibromin acts by negatively modulating the activity of *Ras*, an important intracellular signalling protein critical for regulation of cell growth and survival (figure 8). In addition, neurofibromin is a positive regulator of adenylyl cyclase,<sup>7</sup> the enzyme responsible for the generation of intracellular cyclic AMP (cAMP). Thus, neurofibromin regulates nervous system development along both *Ras*-dependent and cAMP-dependent pathways.

The salient features of our case pertain to endocrine, neurological, radiological and systemic manifestations.

#### Endocrine manifestations

The case we describe presented with confusion and hypoglycaemia in the absence of exogenous insulin use or insulin secretagogues. Testing during hospitalisation showed undetectably low ACTH and cortisol levels, suggesting a central cause for the adrenal insufficiency. In primary adrenal insufficiency caused by lack of adrenal secretion, the ACTH level is elevated and not  $<10$ , as in our case.<sup>8</sup> While the ACTH level was not measured at the time of the CORTROSYN<sup>TM</sup> stimulation test, it is unlikely that it would be totally suppressed by exogenous steroids given

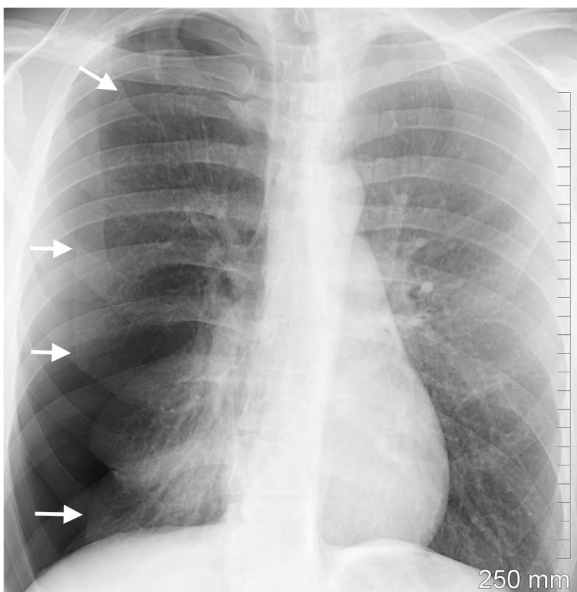




**Figure 5** (A) MRI of the brain—axial T2 fluid-attenuated inversion recovery images at and above the level of the splenium of the corpus callosum demonstrating the sequela of hypoglycaemic injury to the brain. Black arrows indicating focal areas of accentuated abnormal increased signal within the cortex compatible with cortical laminar necrosis. Double black asterisks demonstrating injury to the white matter underlying the cortical injury. The single black asterisk showing the late effects of injury to the left parieto-occipital region with atrophy along the left side of the splenium of the corpus callosum and abnormal increased signal. The single white asterisk indicating mild *ex vacuo* enlargement of the atrium of the left lateral ventricle due to adjacent parenchymal volume loss. (B) MRI of the brain—axial T2-weighted image at location as in (A) demonstrating cortical volume loss (white arrows), injury to the underlying white matter (double white asterisk), atrophy and abnormal increased signal in the splenium of the corpus callosum (single white asterisk) and *ex vacuo* enlargement of the atrium of the left lateral ventricle (single black asterisk).

for <3 weeks. There are several other lines of evidence that support a central cause of the adrenal crisis-like presentation in our case: (1) although primary adrenal insufficiency can cause confusion, hypoglycaemia is more pronounced in hypopituitarism than in hypoadrenalism, due to loss of both cortisol and growth hormone; (2) our case also revealed low levels of insulin-like growth factor-I (IGF-I), a surrogate for growth hormone, which regulates hepatic production of IGF-I; (3) in pituitary-based (central) adrenal insufficiency, hyponatraemia and hypoglycaemia are seen due to loss of ACTH and cortisol, while in primary adrenal insufficiency hyponatraemia and

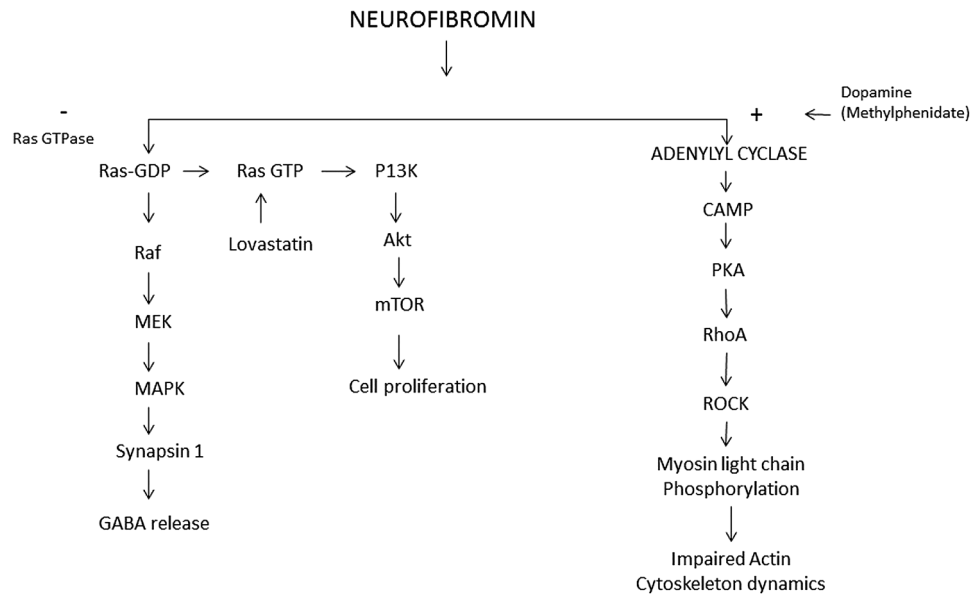
hyperkalaemia (due to mineralocorticoid loss), and hyperpigmentation (due to high-ACTH levels), are more characteristic; our case demonstrated neither hyperkalaemia nor hyperpigmentation and (4) thyroid testing also supported a diagnosis of pituitary-derived adrenal insufficiency. In sick euthyroidism, the thyroid-stimulating hormone (TSH) level is usually normal or low at presentation with low triiodothyronine and low or normal free thyroxine (FT4) levels.<sup>9</sup> In our case, the free hormone levels were lower than normal, but the TSH level was mildly elevated. If this were due to primary hypothyroidism, with a FT4 level of 0.7, the TSH level would be expected to be >15. Furthermore, the undetectable level of thyroperoxidase antibody would argue against a diagnosis of chronic thyroiditis, the most common cause of primary hypothyroidism. However, in panhypopituitarism, the diagnosis is made with low levels of free hormones and low or inappropriately normal TSH due to



**Figure 6** Chest X-ray—frontal projection demonstrating the right-sided pneumothorax (white arrows).



**Figure 7** Chest CT scan—axial lung window showing extensive emphysematous changes with peripheral blebs and bullae anteriorly on the right, indicating by white asterisks.



**Figure 8** Neurofibromin pathways (modified from Diggs-Andrews and Gutmann<sup>24</sup>). Neurofibromin inhibits *Ras*GTPase, which converts inactive *Ras* (bound to GDP) to active *Ras* (*Ras*-GTP); loss of neurofibromin thus results in excessive *Ras* and downstream pathway components, thus promoting upregulated cell growth and tumourigenesis seen as multiple systemic manifestations in neurofibromatosis 1 (NF1). Neurofibromin positively regulates adenylyl cyclase, which is responsible for generation of cAMP; decreased cAMP and components of downstream pathways through impaired cytoskeletal dynamics cause smaller growth cones and attenuated axons. Hypothalamic-pituitary axis involvement in NF1 is explained on the basis of reduced cAMP levels and decreased activation of the cAMP responsive transcription factor (cAMP-response element binding protein, CREB). Cognitive deficits are explained on the basis of: (1) increased GABA release from inhibitory neurons mediated through hyperactivation of *Ras*-dependent MAPK-mediated synapsin 1 phosphorylation, which shifts the balance between excitatory versus inhibitory networks leading to impaired synaptic plasticity required for learning and memory and (2) impaired cAMP-dependent cytoskeletal dynamics and synaptic efficacy. Therapeutic interventions for cognitive and attention deficits might include blocking of *Ras* by lovastatin or release of dopamine by methylphenidate (MAKP, mitogen-activated protein kinases; GABA,  $\gamma$ -aminobutyric acid; mTOR, mammalian target of rapamycin; PKA, protein kinase A).

abnormal glycosylation (although in some cases the TSH level can be elevated, but usually not to >10).<sup>10</sup> Once the adrenal deficiency was addressed in our case, replacement with levothyroxine was started to treat fluid retention and bradycardia, and to improve alertness.

Two critical regulators in the development of the hypothalamic-pituitary axis are cAMP and the transcription factor, cAMP-response element binding protein (CREB).<sup>11</sup> A number of key transcription factors and hormones expressed in the pituitary gland have CREB-binding sites in their promoter regions. Utilising an NF1 mouse model, Hegedus *et al*<sup>12</sup> demonstrated that loss of neurofibromin expression in the hypothalamus decreased cAMP level and CREB activation, resulting in reduced body weight and smaller anterior pituitary glands. These rodents also exhibited reduced GH-releasing hormone, pituitary GH and liver IGF-I production. These data suggest that neurofibromin regulates somatic growth through the hypothalamic-pituitary axis via modulation of cAMP, and this helps explain the panhypopituitarism exhibited in our case.

### Neurological manifestations

Our patient had evidence of left hemispheric stroke-like symptoms and possible seizures. Cerebrovascular and cardiovascular complications of NF1 may manifest at all ages, with reports of stroke as early as 7 weeks of life.<sup>13</sup> Postulated mechanisms include: (1) vasculopathy from loss of neurofibromin expression in endothelial and smooth muscle cells of both intracranial and extracranial vessels, resulting in increased intimal and medial proliferation of vascular smooth muscle cells with malformation or steno-occlusive disease;<sup>14 15</sup> (2) dysregulation of vascular homeostasis, manifesting as hypertension, via loss of neurofibromin expression in circulating, marrow-derived monocytes,

which are critical to the regulation of vascular homeostasis<sup>16</sup> and (3) congenital heart disease, through loss of neurofibromin expression in cardiac myocytes.<sup>17</sup> This improved scientific understanding of the pathogenesis of disease has recently led to the successful use of *Ras* inhibitors, and the kinase inhibitor, imatinib, in mitigation of the neointimal vasculopathy in animal models of NF1 disease.<sup>18</sup> Seizures are also more common in individuals with NF1 than in the general population. They can occur at any age, are typically focal and may be associated with brain tumour or infarction.<sup>19</sup>

An extensive workup in our case failed to identify any specific cause for the left hemispheric stroke-like symptoms and seizures, particularly any unequivocal CNS, cardiac, autoimmune or vasculitis-related aetiology. The abnormal CSF findings, including elevated white cell count and protein, were probably on the basis of a traumatic tap, as calculated using published correction formulas.<sup>20</sup> We ultimately attributed the seizures to severe hypoglycaemia resulting from panhypopituitarism-associated adrenal insufficiency. Once treated for the underlying endocrine abnormalities, our patient remained seizure-free off antiepileptic medications.

### Radiological manifestations

The MRI findings were probably related to hypoglycaemia, aggravated by a prolonged postictal state. While the typical MRI finding in hypoglycaemic encephalopathy is bilateral symmetrical grey and white matter involvement, also reported is restricted diffusion in a focal or unilateral cortical and adjacent subcortical distribution, as seen in our patient.<sup>21 22</sup> The likelihood that the cortical injury in our case was secondary to hypoglycaemia was further supported by the fact that the neuroimaging abnormalities did not conform to a specific

vascular distribution, as would be expected with vascular compromise, but rather occurred in overlapping and multiple vascular territories.

### Systemic manifestations

Other findings in our case included the discovery of plexiform neurofibromas, a sacral spinal canal meningocele and prior episodes of pneumothorax. Plexiform neurofibromas develop in 30–50% of individuals with NF1; they arise from multiple nerve fascicles and can extend into surrounding structures, often causing local bone destruction. This was the likely explanation for the left hip pain and effusion in our case.<sup>23</sup> Sacral spinal canal meningocele, a rare association in NF1, was also discovered in our case but was asymptomatic.

Our detailed case report underscores the need for a careful laboratory assessment to screen for subclinical hypothalamic-pituitary axis involvement in NF1, as well as in symptomatic patients presenting with short stature, hypoglycaemia or signs of adrenal insufficiency. To the best of our knowledge, this is the first report of NF1-associated panhypopituitarism with central adrenal insufficiency presenting as hypoglycaemic seizures and stroke-like symptoms, which are hitherto unreported clinical manifestations of NF1 disease. In such cases, prompt recognition and treatment with hormone supplementation and steroids can prevent devastating complications.

In conclusion, our patient with NF1 displayed many rare and uncommon characteristics of the disease, confirming multisystem involvement. In addition, he also exhibited some novel features of the disease, which could confound the diagnosis of NF1 when determining the aetiology of certain atypical clinical presentations. The combination of these rare systemic features makes this a unique case of NF1, with many important lessons for future diagnosis and even treatment of atypical cases.

### Learning points

- ▶ Hypothalamic-pituitary axis involvement in neurofibromatosis 1 (NF1) can occur in the absence of sellar or suprasellar pathology on brain neuroimaging. Screening for assessment of hypothalamic-pituitary axis involvement in NF1 is recommended in the absence of symptoms of hypopituitarism, as well as in symptomatic patients presenting with short stature, hypoglycaemia or signs of adrenal insufficiency.
- ▶ Genetically engineered NF1 mouse models, together with an understanding of neurofibromin pathways, provide critical insights into the pathogenesis of NF1-associated central and peripheral neurological and systemic manifestations, with many therapeutic implications.
- ▶ Hypoglycaemic encephalopathy can present with stroke-like symptoms. While the typical brain MRI finding in hypoglycaemic encephalopathy is bilateral symmetrical grey and white matter involvement, restricted diffusion in a focal or unilateral cortical and adjacent subcortical distribution is also seen.

**Contributors** WW, MHN, GBA, NB, M. Ali Babi\* and Rup Tandan\* all made substantive contributions to the following: (1) conception and design, acquisition of data, and/or analysis and interpretation of data; (2) Drafting and/or revising the case report for important intellectual content; and (3) Final approval of the manuscript. We have attached the BMJ authorship form including the names and signatures of all five authors (\*Institution/Department and contact information for Drs Babi and Tandan is included with the cover letter that accompanies this submission).

**Competing interests** None declared.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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