

# Hypercalcaemia mimicking Huntington's disease: lessons learned from delayed diagnosis

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## ABSTRACT

Diagnosis can prove challenging when a patient with a chronic neurological disease presents with acute deterioration. This is especially true in Huntington's disease, where cognitive impairment is prominent. We present a case of hypercalcaemia causing an acute deterioration in physical and cognitive function in a patient with Huntington's disease. Similarity in clinical phenotype between hypercalcaemia and Huntington's disease, as well as failure to appreciate the acute nature of the deterioration resulted in diagnostic delay and prolonged admission. With treatment, the patient improved dramatically. The case highlights key learning points regarding assessment of patients with chronic neurological disease.

**KEYWORDS** acute, deterioration, diagnosis, heuristics, Huntington's disease, hypercalcaemia.

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## INTRODUCTION

Huntington's disease (HD) is a trinucleotide repeat disorder. It causes neurodegenerative disease characterised by cognitive decline, neuropsychiatric abnormalities and a movement disorder.<sup>1,2</sup> The disease course of HD is a slowly progressive decline, typically over 15–20 years from diagnosis.<sup>3</sup> Deterioration in motor function and cognition, as well as in brain MRI appearances, is recognised to be gradual and monophasic with no acute deteriorations. This has been supported by longitudinal observational data over 36 months.<sup>3,4</sup> This information is of vital importance when assessing HD patients in the acute setting as any acute deterioration should be assumed to be due to an additional diagnosis. It is tempting for physicians, when confronted with a patient with a serious illness such as HD, to ascribe new symptoms to the known disease. We first wish to emphasise the importance of obtaining the history from all relevant sources in establishing a diagnosis and, second, the improvements that may be made by treatment of intercurrent illness. Here we describe a case of a patient with HD presenting with acute deterioration. The deterioration was initially believed to be due to end-stage HD but proved instead to be hypercalcaemia secondary to primary hyperparathyroidism.

## CASE

A 42-year-old woman, who had been diagnosed with Huntington's disease at the age of 36, was referred by her GP to the medical admissions unit with rash, increased agitation and reduced oral intake. The patient was accompanied by the HD specialist nurse who gave a history of the patient having suffered eight days of vomiting, reduced oral intake, severe constipation and increased confusion, restlessness and insomnia. The HD nurse reported that she had found the patient in bed at home surrounded by feathers, having shredded her duvet. There was also evidence of urinary incontinence. Other than HD there was no other personal or family medical history. Her medications were 10 mg olanzapine at night and 20 mg citalopram once daily. She smoked 20 cigarettes per day and had a history of alcohol excess, having consumed half a bottle of rum per day until six months prior to admission. At the time of admission she was almost abstinent due to lack of money.

On examination she showed evidence of weight loss. She was tachycardic at 115 beats per minute but normotensive and the remainder of the cardiorespiratory examination was normal. She had a palpable goitre and her abdomen was soft and non-tender. Neurological examination revealed that she was oriented to place and person but displayed more prominent choreoathetotic movements than previously documented. She was unable

to stand independently and had a generalised erythematous maculopapular rash, which was thought to be due to exposure to the feathers and urine.

Initial investigation revealed dehydration (sodium 151 mmol/L [135–45 mmol/L], urea 14 mmol/L [2.5–6.6 mmol/L] and creatinine 70  $\mu$ mol/L [60–120  $\mu$ mol/L]), hypercalcaemia (corrected calcium 3.17 mmol/L [2.25–2.5 mmol/L] and subclinical hypothyroidism (TSH 11.63 mU/L [0.20–0.45 mU/L], T4 9.5 pmol/L [9–21 pmol/L]). Her full blood count and C-reactive protein were normal. Her initial management plan consisted of rehydration, enema and referral to dermatology, endocrinology and neurology.

On discussion with the HD nurse, the admitting team revealed their impression was that the overall picture was one of end-stage HD. The HD nurse stressed that just two weeks prior to admission the patient had not been considered near end-stage of her disease. She had been able to mobilise independently, manage her finances and her overall function was such that she was able to travel into town with her friend to attend a local salon with minimal difficulty. The repeat adjusted calcium on day 3 was 2.82 mmol/L yet her hydration status had improved, as evidenced by a normal sodium and urea level. The patient's records were reviewed and there were no previous serum calcium levels available for comparison.

On day 5 of admission the patient was seen by a neurology consultant who reiterated that, despite her appearing as end-stage HD, the time course of deterioration did not follow that expected for HD and that investigation for intercurrent illness was imperative. Following this, the admitting team started levothyroxine, arranged a CT brain scan, ultrasound of the thyroid gland and checked parathyroid hormone levels, which returned at 9.9 nmol/L (normal range 1.6–7.2 pmol/L), thus diagnosing primary hyperparathyroidism. The CT head showed generalised atrophy only and the ultrasound showed moderate enlargement and coarse nodularity of the thyroid gland. On day 11, the endocrinology consultant saw the patient and there was debate over the contribution of hypercalcaemia to the clinical presentation. The result was that a conservative approach with maintenance of hydration and monitoring was planned.

The patient was transferred to a rehabilitation hospital as she could still not mobilise and had continuing problems with constipation, increased choreoathetotic movements and fluctuating confusion. The rehabilitation team noted poor progress with mobility and noted persistently raised corrected calcium levels (2.91 mmol/L) prompting re-referral to endocrinology. Owing to a failure to improve with rehabilitation, she was

reviewed again by the endocrinology consultant, who advised a low calcium diet and cinacalcet, a calcimimetic agent that inhibits parathyroid hormone release. The patient's physical and cognitive function did not begin to improve until a normal corrected calcium level was reached, following titration of cinacalcet dose to 30 mg twice daily. Over four weeks the patient's mobility improved substantially such that she regained independence with walking and most activities of daily living. Her confusion resolved and she was discharged home, where she has since been living with minimal problems for 18 months to date.

## DISCUSSION

Our case reinforces a key diagnostic principle when assessing patients with chronic neurological disease. Despite the clinical features and disease course of HD being well described, diagnostic confusion may occur because of a lack of familiarity with the condition due to its relative rarity.

This case suggests that clinicians' decision making may be subject to bias when confronted with a patient with an unfamiliar medical condition. Thought processes that clinicians use, consciously and subconsciously, to assess probability are called heuristics.<sup>5</sup> These processes can be subject to bias when confronted with data that cannot be comprehensively evaluated due to sample size, complexity or unfamiliarity. One example is representative bias: the more object X is similar to class Y, the more likely we think object X belongs to class Y. In our example, the patient displayed many clinical features of end-stage HD and so this was favoured as the most likely diagnosis despite evidence of intercurrent disease. The diagnostic challenge was increased further by the similarity in clinical features between hypercalcaemia and end-stage HD. The Society for Endocrinology describe several core clinical features of acute hypercalcaemia that are compatible with advanced HD such as mood disturbance, confusion, cognitive dysfunction and muscle weakness.<sup>6</sup> Such similarities create significant diagnostic challenges when looking at the presenting clinical features alone. Indeed, at least 80% of patients with hyperparathyroidism are considered asymptomatic,<sup>7</sup> but may exhibit subtle neuropsychiatric changes or altered quality of life.<sup>8,9</sup>

It should be noted that the patient exhibited subtle signs of hypercalcaemia as well as exaggerated signs of HD. Intercurrent illness is a well-recognised cause of deterioration in the clinical features of neurological diseases including stroke and neurodegenerative disease. This is thought to be related to fragility in compensatory neural networks in these patients. As our case shows, treatment of even modest intercurrent disease may be warranted, as it may produce a marked improvement.

Important categories of intercurrent illness that, in the author's experience, occur more commonly in patients with HD are listed in Table 1.

**CONCLUSION**

The key to accurate diagnosis here was recognising the acute nature of the deterioration as uncharacteristic of the patient's chronic disease. Appreciation of this may have led to earlier diagnosis and treatment, and prevented a prolonged and turbulent admission.

**TABLE 1** Common causes of acute deterioration in patients with HD. The authors consider these conditions more common in patients with HD, but it is not an exhaustive list

| Intercurrent disease | Examples   |
|----------------------|--|
| Infection            | Urinary tract infection<br>Aspiration pneumonia<br>Pressure sores/cellulitis<br>Dental infections  |
| Metabolic            | Electrolyte abnormalities<br>Nutritional deficiencies  |
| Toxic                | Medication side-effects, e.g. <i>akathisia</i> , <i>neuroleptic malignant syndrome</i> , <i>serotonin syndrome</i><br>Poor compliance<br>Alcohol and illegal drugs |
| Other                | Under-treated pain<br>Acute psychiatric illness, e.g. <i>depression</i> , <i>psychosis</i>   |

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