Serotonin syndrome in asymptomatic Huntington’s disease

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Serotonin syndrome is a rare and serious condition most often resulting from iatrogenic insult; the prescriber’s pen is sometimes the most poisonous. Here, Dr Haffenden and Dr Patel discuss a complex case of serotonin syndrome in a patient with genetically proven, but not yet symptomatic, Huntington’s disease and chronic renal impairment. A screening process is proposed to recognise the multitude of precipitating factors, which aligned in this case, and could either alter our prescribing or expedite recognition.

Huntington’s disease (HD), a progressive neurodegenerative disease, is clinically diagnosed with a triad of signs/symptoms: chorea; psychiatric illness, and dementia. Research has shown neurotransmitter deficits in mice models of Huntington’s both before and after symptomatic disease presence—namely a reduction in serotonin. A review of the research demonstrated a few cases of neuroleptic malignant syndrome (NMS) but found no linked cases of serotonin syndrome (SS) and either symptomatic or asymptomatic HD. As such our patient sparked a lot of multidisciplinary interest.

Case presentation
A 53-year-old male was admitted for renal transplant, due to renal failure resulting from an IgA nephropathy, with a creatinine of 1006µmol/L. His surgery was performed using a cadaveric specimen but his postoperative period was complicated by antibody-mediated rejection and steroid-induced psychosis (resolved with reduction of steroids and administration of PRN haloperidol). Six weeks postoperatively the patient was improving and his creatinine had fallen from 1006µmol to 368µmol but he became acutely confused and was wandering the ward naked, tremulous and clammy. Investigations, including bloods, CT head and lumbar puncture, did not uncover the aetiology and he was referred to our liaison psychiatry service for assessment and diagnosis of this acute alteration in his mental state.

Past medical history of note included a genetic, but not yet symptomatic, diagnosis of HD and past psychiatric history included depression, for which he was taking citalopram 20mg once daily. The only other prescribed medication with a psychotropic effect was tramadol, prescribed for analgesia.

Assessment and examination revealed a diaphoresis, bilateral inducible clonus and hyperreflexia, upper limb tremor and expressive dysphasia. Approximately 30 minutes prior to this episode the patient had received a stat dose of the antiemetic ondansetron, 4mg intravenous, as he was feeling nauseated. Blood tests revealed a chronic renal

Figure 1. Hunter’s Criteria (adapted from Boyer and Shannon, 2005)
impairment, hyperkalaemia, hypercalcaemia, anaemia, raised lactate and mild leucocytosis.

With consideration of the symptoms and use of three drugs with a serotonergic action model (citalopram, tramadol and ondansetron) a working diagnosis of serotonin syndrome was made. Management was supportive with cessation of serotonergic agents and IV hydration, and complete recovery was seen after approximately 48 hours.

Discussion
This case highlights an example of serotonin syndrome, a condition resulting in a number of symptoms, including hyperthermia, clonus, diaphoresis, agitation and hyperreflexia. An increased serum serotonin level does not predict the development of serotonin syndrome and cannot be used to aid diagnosis. A useful and accurate diagnostic tool in these patients is Hunter’s criteria as outlined in Figure 1, with a sensitivity of 84% and a specificity of 97% this is now the accepted standard reference tool for diagnosis. Treatment of serotonin syndrome is conservative and supportive with discontinuation of serotonergic agents, active cooling mechanisms for hyperthermia, airway and volume support and benzodiazepines for agitation. This patient’s presentation met the suggested diagnostic criteria for serotonin syndrome given the acute onset of neuropsychiatric symptoms and resolution of symptoms upon cessation of serotonergic agents in the absence of any alternative medical aetiology.

Although some of the literature refutes the role of ondansetron in the development of serotonin syndrome a clear temporal association between ondansetron treatment and onset of serotonin toxicity is demonstrated here in a neurologically vulnerable patient. There have been case reports of the development of serotonin syndrome in patients with a previous psychiatric history who were given ondansetron, linked to the concomitant use of pro-serotonergic medications, but again highlighting the role of ondansetron in patients who are predisposed to neurotransmitter deficit.

We feel our case highlights the combination of several predisposing factors making this patient more vulnerable to the use of multiple serotonergic agents. These include:

- **Factors affecting renal clearance** – Reduced renal clearance leads to higher circulating plasma concentrations of serotonin. With a chronic renal impairment it is likely our patient was not able to clear serotonin as one would expect.
- **Neurodegenerative conditions** – There is evidence in the literature to suggest that patients with a neurodegenerative condition such as Parkinson’s disease are predisposed to the development of serotonin syndrome. Perhaps an already vulnerable brain is more easily influenced by small changes in neurotransmitters. We postulate that the same is the case with HD; although no reported cases were found on review of the literature, we were able to find evidence of cases associating the equally lethal condition of NMS in four patients with HD.

This complex interplay also emphasises the desirability of a medication interaction checking tool to aid safe prescribing. With knowledge of these enzymes and the emerging use of mechanistic models in predicting drug-drug interactions we may in the future be able to predict severe adverse reactions in specific patient populations.

**Implications for clinical care**
Our case not only adds to the literature a previously unpublished case of serotonin syndrome associated with HD. It also usefully illustrates multiple predisposing and precipitating factors occurring together, that have been previously implicated individually, in the development of serotonin syndrome. Dissecting out these factors in an attempt to discover why our patient developed serotonin syndrome helps to formulate a checklist that can prompt clinicians to consider their prescribing decisions. In the age of electronic prescribing this could be an automated algorithm that produces an alert with the prescription of two or more serotonergic drugs with increasing severity dependent on the patient’s creatinine, neurological vulnerability and psychiatric history. Frequent prompting in this manner would also increase awareness of serotonin syndrome amongst prescribers and thus potentially expedite diagnosis and subsequent cessation of serotonergic agents.
Conclusion
This case raises several points that are of clinical importance. Firstly, it acts as a reminder of the serious and potentially fatal serotonin syndrome. Secondly, it highlights the need for adequate risk assessment prior to the prescription of a serotonergic agent. Perhaps in the future that risk assessment will be guided by the use of mechanistic physiologically-based pharmacokinetic models, but for now heightened awareness of serotonin syndrome and the routine use of a drug interaction checker would be of benefit.

Dr Haffenden is a Foundation Year 2 Doctor and Dr Patel is a Consultant Liaison Psychiatrist, both at NBT Mental Health Liaison Team, Southmead Hospital, Bristol.

Declaration of interests
No conflicts of interest were declared.

References