Serotonin syndrome: take a closer look at the unwell surgical patient

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ABSTRACT

This article describes the sequence of acute clinical deterioration seen in a head and neck oncology patient who developed serotonin syndrome perioperatively. It highlights the clinical dilemma that can be encountered when a septic picture masks the onset of serotonin syndrome and reinforces the importance of awareness of the potential interactions and side effects associated with drugs that surgeons prescribe. We discuss the pathophysiology, causal factors, clinical presentation and diagnosis of serotonin syndrome as well as highlighting some of the dilemmas that this condition presents in the surgical setting.

KEYWORDS

Serotonin syndrome – Oncology – Head and neck surgery

Accepted 22 February 2011

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This paper shows how a difficult case can prompt a literature review that teaches all of us something new and clinically relevant. Surgeons of all specialties may come across this syndrome once in their career. We hope that this case-based review may help them recognise it. If you feel you could

submit a similar case-based review, please contact the Editor before you prepare the manuscript.

COLIN JOHNSON
Editor-in-Chief

Case history

Mr K is a 77-year-old patient admitted for a hemimaxillectomy for a primary squamous carcinoma of the palate. His co-morbidities were insulin-dependant diabetes, hypertension, mild depression and chronic lymphoedema. Preoperatively, all blood tests were normal. His diabetic control was reviewed and optimised. A week after the uneventful operation, the patient developed acute depression for which fluoxetine was prescribed. Three days after starting the selective serotonin reuptake inhibitor (SSRI), Mr K developed a neutrophilia and swinging pyrexia.

A swab of a gangrenous toe grew methicillin-resistant *Staphylococcus aureus* (MRSA) but three blood cultures were negative. As there was radiological and clinical evidence of early osteomyelitis, intravenous vancomycin and rifampicin were started. When no improvement was seen after four days and a blood culture grew MRSA, microbiologists advised to start the anti-MRSA antibiotic linezolid. Over the next 48 hours Mr K became increasingly agitated and confused. His pyrexia persisted and was accompanied simultaneously by hypertension, tachycardia, rigors, ataxia, agitation and insomnia, which all worsened over

the next 72 hours. A neurological examination revealed generalised hypertonicity and weakness of all limbs with intact sensation in the upper limbs and an unchanged diabetic neuropathy in his lower limbs. Coordination and proprioception could not be tested due to the patient's confusion but there were no signs of cerebrovascular events. Inducible clonus was present in both feet and reflexes were generally brisk.

A medical review suggested sepsis from the gangrenous toe as the underlying cause of his pyrexia, agitation and neurological signs so this toe was amputated. Type 2 respiratory failure and reduced consciousness in the recovery room led to reintubation and admission to the intensive care unit (ICU). An urgent CT scan performed after admission to the ICU excluded a stroke. A critical review of the physiological (tachycardia, $>39^{\circ}\text{C}$ pyrexia, persistent hypertension of $>220\text{mmHg}$ systolic), neurological (clonus, hyperreflexia, confusion, agitation and insomnia) and vegetative symptoms led to the differential diagnosis of serotonin syndrome (SS). All serotonergic drugs were stopped and management was purely supportive. Mr K was extubated four days later. He remained drowsy for a further week. Over the next two months he made a full physical and mental recovery.

Table 1 Comparison of the Sternbach and Hunter diagnostic criteria for serotonin syndrome (SS)

Diagnostic criteria	Clinical features required	Sensitivity/specificity ⁴
Sternbach ²	1. Recent addition or increase in a known serotonergic agent 2. Absence of other possible aetiologies (infection, substance abuse, withdrawal etc) 3. No recent addition or increase of a neuroleptic agent 4. At least 3 of the following symptoms: <ul style="list-style-type: none"> • mental status changes (confusion, hypomania) • agitation • myoclonus • hyperreflexia • diaphoresis • shivering • tremor • diarrhoea • incoordination • fever 	75% / 96%
Hunter ³	In the presence of a serotonergic agent: <ol style="list-style-type: none"> 1. spontaneous clonus = SS 2. ELSE IF inducible clonus AND agitation OR diaphoresis = SS 3. ELSE IF ocular clonus AND agitation OR diaphoresis = SS 4. ELSE IF tremor AND hyperreflexia = SS 5. ELSE IF hypertonic AND pyrexia >38°C AND ocular clonus OR inducible clonus = SS 6. ELSE NOT SS 	84% / 97%

Introduction and epidemiology

SS is a drug-induced condition that results from the effects of toxic levels of the neurotransmitter serotonin (5-HT). It is a spectrum disorder and although the classical clinical picture encompasses the triad of mental state changes (agitation, confusion), autonomic hyperactivity (sweating, fever, tachycardia, tachypnoea) and neuromuscular abnormalities (tremor, clonus, hyperreflexia and rigidity), in many cases all three do not manifest concomitantly; SS can therefore be difficult to diagnose. As 85% of UK practitioners do not know about SS at all¹ the true incidence of SS is unknown.

Diagnosis

SS is a clinical diagnosis. The classification by Sternbach² (Table 1) used a list of symptoms for diagnosis but by not stressing the importance of the clinical triad of autonomic

signs, neuromuscular change and altered mental state, it allowed for reporting bias that leaned towards mental state changes and hence carried the risk of misdiagnosis. To resolve this, the Hunter SS criteria were devised⁵ (Table 1) so that only clonus, agitation, sweating, tremor and hyperreflexia are needed in the presence of a serotonergic agent to diagnose SS.

Pathophysiology

The physiological actions of serotonin are diverse; it has been implicated in learning and memory, behaviour, thermoregulation, sexual function, hormonal secretions, pain perception and immune response.

Serotonin is a monoamine neurotransmitter that is synthesised in presynaptic neurones from the precursor tryptophan. Serotonin is released into the synapse and acts on specialised 5-HT receptors on postsynaptic neurones. There are seven principle types of 5-HT receptor, several of which have further subtypes. The subtype currently believed to be most implicated in SS is 5-HT_{2A}.^{5,6} Although 5-HT_{1A} has also been implicated in several papers, there is evidence showing that the selective blockade of 5-HT_{1A} has been either ineffectual or has resulted in worsening of the symptoms (Table 2).^{8,9}

Figure 1 illustrates the mechanisms of SS. The synaptic 5-HT that is not required is reabsorbed into the presynaptic neurone via a transporter mechanism. After reuptake, serotonin is metabolised into 5-hydroxyindoleacetic acid by the enzymes monoamine oxydase and catechol-O-methyl transferase and excreted renally. Inhibition of serotonin reuptake, eg by SSRIs, tricyclics or opiates, or inhibited metabolism by monoamine oxidase inhibitors (MAOIs) result in increased levels of 5-HT and hyperstimulation of the postsynaptic receptors.

Table 2 Role of serotonin (5-HT) receptor subtypes in relation to serotonin syndrome

Receptor	Action related to serotonin syndrome
5-HT _{1A}	Neuronal inhibition, sleep regulation, appetite, thermoregulation, anxiety and hyperactivity, depression with hypoactivity
5-HT _{1D}	Locomotion, muscle tone
5-HT _{2A}	Neuronal excitation, learning, peripheral vasoconstriction, platelet aggregation
5-HT _{2B}	Stomach contraction
5-HT ₃	Nausea and vomiting, anxiety

From Boyer and Shannon⁷

Table 3 Causal agents in serotonin syndrome and their mechanism of action^{5,8,10-13}

Mechanism of action	Classification of agent		Example	
Increased serotonin production or release	1.	Food supplements	1.	L-tryptophan
	2.	Illicit drugs	2.	Ecstasy (MDMA) Amphetamines
Increased stimulation of postsynaptic receptor	1.	Anxiolytics	1.	Buspirone
	2.	Mood stabilisers	2.	Lithium
Inhibition of serotonin reuptake	1.	SSRIs	1.	Citalopram Sertraline Fluoxetine Trazodone Imipramine
	2.	Tricyclic antidepressants	2.	
	3.	Opiates	3.	Tramadol Fentanyl Methadone Pentazocine Pethidine
	4.	Antihistamines	4.	Chlorphenamine
	5.	Alternative medicine	5.	St John's wort
Inhibition of serotonin metabolism	1.	MAOIs: antidepressant		Moclobemide Phenelzine Iproniazid Selegiline Linezolid Procarbazine
		antiparkinsonian antimicrobial anticancer		

Causal agents

Causal agents for SS can be divided into four subgroups (Table 3). SS can occur as part of monotherapy, eg SSRIs or MAOIs, or as a result of combination therapies. It is now recognised that SS is a dose-effect response that is not only related to the dose of medication but also variability in cytochrome P450 enzyme activity, which in turn leads to increased or decreased susceptibility to SS.⁴

In surgical practice, many patients are prescribed opiates perioperatively. Several opioids are serotonin reuptake inhibitors (SRIs) although there is a suggestion that tramadol and pethidine may also stimulate serotonin release.⁸ Opioids, which do not trigger SS, include morphine, oxycodone and buprenorphine, whereas fentanyl, pethidine, tramadol, methadone and dextromethorphan are all weak SRIs and can precipitate SS in conjunction with MAOIs or SSRIs.^{8,10}

There are several 'hidden' MAOIs in clinical practice that have been elucidated through SS. One is methylene blue, which is used in parathyroid surgery.¹² Several cases of SS have been documented in patients who were previously on SSRIs and were administered methylene blue intraoperatively. Another is linezolid, an MAOI antimicrobial used in the treatment of Gram-positive infections including MRSA, vancomycin-resistant *Enterococcus* and severe hospital-acquired pneumonia. There have been several cases of life-threatening SS associated with its use.^{15,14}

Tricyclic antidepressants are SRIs and can therefore precipitate SS when combined with MAOIs. The most potent of this group are clomipramine and imipramine, which have both been associated with life-threatening SS.^{5,15} Am-

itriptyline, commonly used in pain management in surgical patients, is less potent and has been shown to be safe in combination with MAOIs.¹⁵

The antihistamine chlorphenamine has SRI activity and could theoretically precipitate SS.⁸ To date there are no documented cases of severe SS in relation to chlorphenamine but this may just be related to the lack of awareness of its SRI activity.

Clinical implications for the surgeon

The clinical features of SS can be confused with other conditions in surgical patients such as neuroleptic malignant syndrome (NMS), alcohol withdrawal (delirium tremens), malignant hyperpyrexia and sepsis associated encephalopathy (SAE) (Table 4). Although it is unusual for surgeons to prescribe neuroleptic medication, NMS can result from any medication that potentially increases dopamine levels,¹⁶ such as metoclopramide, or the sudden withdrawal of antiparkinsonian medication in patients who are nil-by-mouth or acutely unwell.

Alcohol and opiate withdrawal can confuse a clinical picture as it occurs 2–3 days after admission and hence in the postoperative period. Restlessness, hallucinations, normal reflexes and the absence of infections are key signs of delirium tremens.^{17,18}

Septic encephalopathy can mimic SS in the acute phase. In the surgical patient who may be on tramadol and an SSRI, the possibility of the two diagnoses occurring simultaneously must be considered. Drug-related permanent brain damage is well documented in SAE and the coexistence of SS is likely to be a factor in a worsening prognosis.²⁰

Conclusions

There are numerous case reports and reviews of SS in the medical literature that highlight the dangers of serotonergic medication in high doses or in combination. SS is a spectrum, dose-effect response that can be life-threatening. However, if diagnosed, it is reversible. The diagnosis of SS requires awareness of the condition, an understanding of the pharmacology of the drugs that we prescribe and an approach to excluding differential diagnoses.

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Table 4 Distinguishing between SS and other differential diagnoses in the surgical patient^{5,7,16–20}

	SS	NMS	SAE	DT	MH
Onset	Rapid after start/increase of serotonergic agent	Slower; ≤7days after start of neuroleptic agent	Slower; preceded by systemic inflammatory response syndrome and septic blood picture	48–72 hrs after last alcohol intake	Very rapid; either during or in the recovery phase after general anaesthetic
Symptoms	Agitation, diarrhoea	Hypersalivation; incontinence	Agitation, confusion, altered sleep/wake pattern, impaired attention	Psychomotor agitation, zoopsia	Not applicable if unconscious; if conscious: fever, confusion
Signs	Clonus, hyperkinesia, hyperreflexia, pyramidal hypertonicity	Extrapyramidal rigidity, rhabdomyolysis (increased creatine kinase), bradykinesia	Fluctuating confusion progressing to coma, haemodynamic instability, loss of deep tendon reflexes, rigidity, myoclonus; blood picture of infection	Hyperpyrexia, tachycardia, hypertension	Rapidly increasing pyrexia, severe muscular rigidity, tachycardia +++, hypercapnia, rhabdomyolysis

SS = serotonin syndrome; NMS = neuroleptic malignant syndrome; SAE = sepsis associated encephalopathy; DT = delirium tremens; MH = malignant hyperpyrexia