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Review Article

Internal Medicine Section

Controversies in Serotonin Syndrome Diagnosis and Management: A Review

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ABSTRACT

Over the past few years, Serotonin Syndrome (SS) has become a significant clinical concern. Over the last decade, United States saw a surge in antidepressant use. SS characteristically presents as the triad of altered mental status, autonomic dysfunction and neuromuscular excitation. Symptoms vary from patient to patient with mild cases presenting with subacute symptoms and severe cases progressing rapidly to death. Due to the protean manifestations of the syndrome along with non-specific prodromal, SS can easily be misdiagnosed if not carefully assessed. In severe cases, SS can be mistaken as neuroleptic malignant syndrome while mild cases are mostly misattributed to other causes such as flu. SS is a clinical diagnosis and therefore, requires a thorough review of medications and physical examination. Given the protean nature of this toxicologic syndrome various criteria were defined which includes Sternbach's, Radomski and Hunter's criteria. Keeping in mind the wide symptoms of serotonin syndrome from being barely perceptible to lethal emphasis there is a need to treat the syndrome on urgent basis. Mainstay for treatment of serotonin syndrome is to discontinue the offending drug. Improvement is seen in most patients within 24 hours.

Keywords: Controversies, Neuroleptic malignant syndrome, Serotonin syndrome

What is Serotonin Syndrome?

Over the past few years, SS has become a significant clinical concern. In the last decade, United States saw a surge in antidepressant use. By 1999, around 6% of adults were taking antidepressants; in just a decade (2010), the percentage had increased to 10.4% [1]. Even there was a surge in US poison control centers where there was almost a 15% increase in ingestions of Selective Serotonin Reuptake Inhibitors (SSRIs) from 2002 to 2005 [2,3]. However, SS should not be considered as an extremely rare idiosyncratic reaction to medication, unlike Neuroleptic Malignant Syndrome (NMS). It is due to an increase in concentration levels of serotonergic toxins irrespective of age [4]. However, the true incidence of SS is underestimated for a number of reasons. Most common reasons include mild cases being dismissed; clinicians may not suspect the condition or manifestations may be wrongly attributed to another cause.

How does it Present?

SS characteristically presents as the triad of altered mental status, autonomic dysfunction and neuromuscular excitation. However, these symptoms may not occur simultaneously: altered mental status and autonomic dysfunction is present in roughly 40% of the cases and neuromuscular excitation in 50% [5]. Symptoms of toxicity with serotonergic agents arise within an hour of a precipitating event in approximately 30% of patients, and within six hours in 60% [6]. One of the key diagnostic features includes spontaneous/induced clonus and hyperreflexia which is generally more pronounced in the lower limbs [7]. Symptoms may vary from patient to patient with mild cases presenting with subacute symptoms and severe cases progressing rapidly to death.

Diagnostic Criteria

Due to the protean manifestations of the syndrome along with non-specific prodromal, SS can easily be misdiagnosed if not carefully assessed. In severe cases, SS can be mistaken as NMS while mild cases are mostly misattributed to other causes such as flu. SS is a clinical diagnosis and therefore, requires a thorough review of medications and physical examination. Serum serotonin levels are an unreliable indicator of toxicity and do not correlate well with the clinical presentation [6]. The Sternbach criteria are less specific (96% vs 97%) and less sensitive (75% vs 84%) as compared to the Hunter's criteria [1]. Sternbach's criteria are also more likely to yield a false-positive result [7].

Firstly, the syndrome may be missed because of its protean manifestations. Clinicians and physicians may dismiss symptoms such as tremor with diarrhoea or hypertension as inconsequential or unrelated to drug therapy; anxiety and akathisia may be misattributed to the patient's mental status. Secondly, a strict application of the diagnostic criteria meant more true negatives as well as false positives.

Neuroleptic Malignant Syndrome, which often times mimics serotonin syndrome, also develops over days to weeks [8,9]. Besides, in 70% of the patients, clinical signs including agitated delirium with confusion appear first, followed by tremors, rigidity, hyperthermia, profuse diaphoresis and tachypnoea [10-12]. Key things to look forward in distinguishing Neuroleptic Malignant Syndrome from serotonin syndrome is the absence of clonus, bradyreflexia and the timeline of the clinical course. Some of the typical prodromal symptoms like nausea and vomiting are also rare in Neuroleptic Malignant Syndrome [13].

Diagnostic controversies (Sternbach's, Radomski's and Hunter's Criteria)

Given the protean nature of this toxicologic syndrome various criteria were defined which includes Sternbach's, Radomski and Hunter's criteria.

Sternbach's Criteria

The first classification to be published regarding the syndrome was Sternbach's criteria which was published in 1999, based on

38 psychiatric inpatients [9]. The Sternbach's criteria included the following:

• At least three of the following physical findings are present: agitation, diaphoresis, ataxia, diarrhoea, mental status changes, hyperreflexia, myoclonus, tremor, shivering, or hyperthermia;

• Other common aetiologies, such as intoxication, infection, metabolic derangements, substance abuse, and withdrawal have been ruled out. Also, no neuroleptic agent should have been added recently.

One of the key points heavily criticized was the fact that Sternbach's criteria was too unspecific. It was relying too much on mental status changes evident from the fact that the criteria could indicate serotonin syndrome in a patient presenting with agitation, confusion or hyperthermia, without any neuromuscular symptoms. Also, many of the 10 clinical features suggested as typical of serotonin toxicity by Sternbach were non-specific. These would also be commonly observed in many other conditions such as anticholinergic delirium, and alcohol and drug withdrawal states. Also, sternbach's clinical definition was based on case reports and small published case series. Sternbach recognised that the features were non-specific. He thought that other possible causes of the features must be excluded. Therefore, it is widely accepted that sternbach's criteria cannot be used for differential diagnosis; however, it still remains a useful tool in early recognition of the syndrome. Besides, the criteria are also not useful in identifying newer drugs as the cause of serotonin toxicity. In addition, many of the proposed 10 diagnostic features of the criteria can occur with other common toxidromes including catecholamine excess. Hence, the original idea of sternbach's criteria being relied on to diagnose serotonin syndrome can be refuted.

Radomski's Criteria

In the year 2001, Radomski refined Sternbach's criteria based on a review of 62 inpatient psychiatric cases, including Sternbach's original 38 cases [9]. He differentiated between many symptoms of serotonin syndrome on the basis of severity and added "rigidity" to the neuromuscular symptoms criteria. His criteria included,

• Simultaneous occurrence of four major or three major and two minor criteria for adding or increasing the dose of a serotonin-acting drug;

• The clinical symptoms were not part of an underlying psychiatric illness that existed when a serotonergic agent was administered;

• Other possible aetiologies are excluded;

• There is no neuroleptic drug in dosage started or increased prior to the symptoms.

Radomski's criteria used similar clinical features as sternbach's criteria; however, it was more precisely focussed to gauge the severity of serotonin syndrome rather than diagnosing it.

Hunter's Criteria

Two years after the Radomski criteria was released, Dunkley et al., released the Hunter's criteria based on a review of 2222 cases of overdoses with SSRIs, in the year 2005 [9]. Focusing mainly on neuromuscular symptoms, the classification introduced clonus in its various forms. At the same time, Hunter removed myoclonus from the symptom list. Also, hunter's criteria originators claimed that their criteria were far more specific and sensitive than the other two classification systems.

Pros of Hunter's Criteria:

• Hunter's Criteria gave a decision tree for diagnosing SS in patients having clinical features that were significantly associated with patients diagnosed by a clinical toxicologist to have serotonin toxicity.

• To reduce the confounding effects of co-ingested drugs with other than serotonergic actions, the dataset of overdoses of a single SSRI was obtained. This was done to obtain features arising from a purely serotonergic drug and also to check the sensitivity and specificity of the decision rules. The dataset was also searched for life-threatening cases to determine which features were associated with severe serotonin toxicity.

• Only a few well-defined clinical features were used in Hunter's Criteria (hypertonia, agitation, tremor, hyperreflexia, temperature and clonus). Clonus is the most important sign in the Hunter's Criteria. This neuromuscular feature was strongly associated with serotonin toxicity. All types of clonus were common and significantly associated with all three outcomes in the SSRI alone overdoses.

• Reduction in the number of mental status criteria used to determine serotonin toxicity, making the criteria more sensitive to features of serotonin toxicity. This should also reduce the number of other conditions such as anticholinergic and other drug-induced deliriums reaching the diagnostic criteria for serotonin toxicity, hence, making the criteria more sensitive.

• Rigidity did not occur in any of the patients in the original SSRI dataset, but this was recognized in a previous study of SSRI poisoning. Its inclusion was based on its frequent occurrence in cases of life-threatening serotonin toxicity in the literature. Because of its clinical importance, hypertonicity/rigidity was felt to be a mandatory inclusion in the final decision rule.

• Tachycardia and Mydriasis may not be a useful diagnostic signs as they are commonly seen in many drug overdoses including anticholinergic drugs, however, they are very useful in the management of patients who are already diagnosed with serotonin toxicity.

Cons of Hunter's Criteria

• Since, Hunter's Criteria was exclusively derived from SSRI overdose conditions, minor cases including patients presenting with autonomic instability can easily be missed if this criteria was used, which could lead to rapid deterioration of patient condition.

• Some patients with neurological pathologies (such as peripheral neuropathy) may not be presenting with characteristic symptoms of the criteria since nerve damage may mask upper motor neuron signs like hyperreflexia/clonus. Besides, reflexes or clonus may not be elicitable in patients with severe SS who have developed substantial muscle rigidity.

• Common features for both Neuroleptic Maligant Syndrome and serotonin syndrome include muscle rigidity, metabolic acidosis, leukocytosis and elevated hepatic transaminases, which highlight the necessity of a thorough history and physical examination.

• External validation of the decision rules in different settings including emergency departments and toxicology treatment centers are needed. Studies demonstrating the effectiveness of these decisions in treatment outcomes are needed, as well.

Management

Keeping in mind the wide variety of symptoms of serotonin syndrome, its treatment should be started on urgent basis, as delay can be lethal. The two mainstays of serotonin syndrome management are to discontinue the serotonergic agent and to give supportive care. Most patients improve within 24 hours of cessation of the precipitating drug and starting the therapy [6].

Management of serotonin syndrome includes some basic principles and guidelines as mentioned:

• Discontinuation of all serotonergic agents;

• Supportive care aimed at normalization of vital signs;

• Sedation with benzodiazepines;

• Administration of serotonin antagonists.

Application of these principles varies with the severity of illness. In mild cases, discontinuation of inciting medications, supportive care, and sedation with benzodiazepines is generally sufficient. Moderately ill patients require more aggressive treatment of autonomic instability (including continuous hyperthermia, tachycardia, muscle rigidity and dizziness). Severe cases need rigorous management by supportive care and endotracheal tube intubation. Hence, in severe cases sedation with benzodiazepines can be used for controlling agitation as well as, correcting mild increase in blood pressure and heart rate. However, management of autonomic instability may be difficult; severely intoxicated patients often exhibit rapid, dramatic changes in vital signs.

Control of hyperthermia is also critical and involves eliminating excessive muscle activity. For patients whose temperature is above 41.1°C, recommended treatment includes immediate sedation, paralysis, and tracheal intubation.

If supportive care and benzodiazepines fail to correct vital signs and improve agitation, treatment with cyproheptadine is the best option [4]. However, special caution should be taken with cyproheptadine as it may lead to sedation and transient hypotension that is responsive to intravenous fluids [4].

CONCLUSION

Over the past few years, serotonin syndrome has become a significant clinical concern especially with a surge in antidepressant use. Keeping in mind the wide symptoms of serotonin syndrome there is a need to treat the syndrome on urgent basis. Nevertheless, even with major improvements in the recent years for the management of serotonin syndrome, still there are some concerns regarding the outcome of these drugs at long-term observation. For the same reason, conventional drugs remain the treatment of choice for serotonin syndrome. However, larger studies with long-term follow-up are needed to adequately address the safety and efficacy issues in the management of serotonin syndrome, especially with the prevalence of anti-depressants in our society.

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