

[ ORIGINAL ARTICLE ]

# Malignant Syndrome and Serotonin Syndrome in a General Hospital Setting: Clinical Features, Frequency and Prognosis

Akiyuki Hiraga<sup>1</sup> and Satoshi Kuwabara<sup>2</sup>

## Abstract:

**Objective** The differences in the frequency and clinical features of malignant syndrome (MS) and serotonin syndrome (SS) in same population have only rarely been reported. To report the frequency and clinical features of MS and SS in a general hospital setting.

**Methods** The clinical and laboratory features of patients with MS and those with SS, who were consecutively admitted to Chiba Rosai Hospital, during the past 4.5 years were reviewed.

**Results** Of the 2005 patients admitted, MS was observed in 16 patients (0.8%) and SS in 2 (0.1%). In the 16 patients with MS, the underlying disorder included depression (n = 5), and dementia or parkinsonism (n = 11). The underlying etiology of the 2 patients with SS was depression. In 5 patients, MS was difficult to distinguish from SS because of overlapping symptoms and signs and/or treatments with both neuroleptic and serotonergic drugs. Of the 16 patients with MS, 1 died, 1 remained wheelchair-bound, 4 were able to walk with assistance, and 10 regained their ability to ambulate independently. The 2 patients with SS recovered after cyproheptadine therapy and were discharged on foot.

**Conclusion** MS occurs more frequently than SS in the general hospital setting. Underlying aetiologies in patients with MS were more common due to dementia or parkinsonism than in patients with psychiatric disorders. The differential diagnosis of MS and SS is often difficult and the diagnostic sensitivities largely differ for each of the diagnostic criteria. As a result, the establishment of new diagnostic criteria that specifically focus on distinguishing MS from SS is therefore required.

**Key words:** malignant syndrome, serotonin syndrome, psychiatrics, serotonergic agents, parkinsonism, dementia

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## Introduction

Malignant syndrome (MS) and serotonin syndrome (SS) occur as a result of adverse reactions to drugs used for treating schizophrenia and depression. MS mainly develops while using neuroleptics, whereas SS mainly occurs because of the use of serotonergic antidepressants. Although both syndromes present with different symptoms, they cause similar symptoms and signs, including an acute onset of hyperthermia, altered mentation/consciousness, motor symptoms, and autonomic symptoms (1, 2). MS was originally

described in patients receiving neuroleptics (neuroleptic MS) and has subsequently been reported in those with Parkinson disease (PD) (3). The rates and prognosis of MS and SS may vary considerably among countries and hospital settings (general vs. mental hospitals). Most previous studies regarding MS and SS have been conducted in psychiatric departments, and the current literature concerning MS and SS in general hospitals is very scarce and limited. Moreover, the differences in the frequency and clinical features of MS and SS in the same population have only rarely been reported. We herein report the frequency and clinical features of MS and SS in a general hospital setting.

<sup>1</sup>Department of Neurology, Chiba Rosai Hospital, Japan and <sup>2</sup>Department of Neurology, Graduate School of Medicine, Chiba University, Japan  
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Correspondence to Dr. Akiyuki Hiraga, hiragaa@yahoo.co.jp

## Materials and Methods

### Patients

The medical records of patients (n = 2005) who were diagnosed with MS and SS and who were admitted to the neurological department of Chiba Rosai Hospital (a total of 48,214 patients were admitted to this 400-bed acute general hospital that caters to a population of 280,000 inhabitants) between April 2010 and September 2014 were retrospectively reviewed. Our institution has an outpatient clinic, but no inpatient beds for patients with psychiatric disorders. Therefore, patients with MS and SS were admitted to the neurological department. Moreover, patients with MS and SS were admitted to our department from nearby psychiatric clinics. All the patients were re-evaluated for the clinical features of MS, according to the criteria of Levenson (1985) (4), Pope et al. (1986) (5), and Caroff and Mann (1993) (6), and those of SS, according to Sternbach (1998) (7) and Birmes et al. (2003) (8). In patients with parkinsonism, rigidity because of MS or SS improves after treatment. Elevated creatine kinase (CK) levels, secondary to MS or SS, have been reported when the serum CK levels increased to >2 times the upper limit of our normal laboratory range (43-165 U/L). Patients with a history of trauma, intramuscular injections, myocardial infarction, drug abuse, or hypothyroidism were excluded because these conditions can induce an increase in CK levels independent of MS or SS. Patients who presented with increased baseline CK levels at previous examinations were also excluded.

### Laboratory testing

Blood cell counts and routine blood chemistry tests, including those for CK, were performed during the first neurological examination. These laboratory tests were serially performed.

### Treatment

General supportive treatments, such as hydration, nutrition, reduction of fever, and discontinuation of any neuroleptic agent or precipitating drug were considered essential. Each responsible neurologist made the final decision regarding the treatment using bromocriptine (dopamine agonist), dantrolene (skeletal muscle relaxant), and cyproheptadine (serotonin antagonist).

## Results

### Frequency and background disease

While observing 2005 patients, MS was observed in 16 patients (0.8%; n = 8 men and n = 8 women; mean age, 65 years) and SS was observed in two patients (0.1%; n = 1 man and n = 1 woman; mean age, 38 years). One of the 16 patients developed MS 2 days after admission.

In the 16 patients with MS, the underlying etiologies were as follows: depression (n = 5), PD (n = 4), Alzheimer disease (n = 2), progressive supranuclear palsy (n = 2), dementia with Lewy bodies (DLB; n = 1), other undiagnosed dementia (n = 1), and other undiagnosed parkinsonism (n = 1). The underlying etiology of the two patients with SS was depression. Of the 16 patients with MS, 11 received the following psychiatric medications: typical antipsychotics (n = 5), atypical antipsychotics (n = 5), tricyclic antidepressants (TCAs) (n = 1), tetracyclic antidepressants (n = 1), selective serotonin reuptake inhibitors (SSRIs) (n = 3), and serotonin and norepinephrine reuptake inhibitors (SNRIs) (n = 3). In addition, the two patients with SS received atypical antipsychotics (n = 1), TCAs (n = 1), SSRIs (n = 2), and SNRIs (n = 1). One patient with SS was treated with SSRIs and SNRIs, whereas the other patient was treated with two SSRIs. One of the 16 patients with MS having PD was treated with a selective monoamine oxidase (MAO-B) inhibitor. In patients with parkinsonism, including those with PD presenting with MS, six received anti-parkinsonian drugs; however, levodopa was discontinued in only one patient, while in the other patients, anti-parkinsonian drugs were not discontinued and the doses were not abruptly decreased.

### Clinical features and association with the diagnostic criteria

The clinical features of patients with MS and SS are provided in Table 1. Atypical features were as follows: generalized seizure and reversible cardiomyopathy in acute phase and ataxia in recovery phase in patients with MS (n = 1) and dysarthria and numbness (n = 1) and ophthalmoplegia (n = 1) in patients with SS. The white blood cell (WBC) count was elevated in 11 of the 16 patients with MS at admission (mean, 11,737; range, 4,000-28,700) and in both patients with SS (mean, 9,800; range, 8,900-10,700). The mean serum creatinine levels were 1.1 mg/dL (range, 0.5-3.5 mg/dL) in patients with MS and 0.8 mg/dL (range, 0.7-0.8 mg/dL) in patients with SS. In patients with MS, the mean serum CK level was 2,709 U/L at admission, which was significantly higher than that in those with SS (129 U/L). Seven of 16 patients with MS had increased CK levels after admission.

According to the diagnostic criteria, all 16 patients with MS fulfilled the criteria of Levenson; however, only four patients fulfilled the criteria of Caroff (Table 2). According to the criteria of Pope, eight of 16 patients had definite MS, whereas three had probable MS. Of 16 patients with MS, MS was difficult to diagnose in five because only the clinical features were noted. Furthermore, two of these five patients did not receive any serotonergic agents, thus making it difficult to distinguish MS from SS. The other three patients with MS received drugs that induced MS and serotonergic drugs, thereby fulfilling the criteria for MS and SS. In these three patients, the maximum CK levels were 783, 5,203, and 10,065, and WBC counts (elevated) were 10,600, 14,900,

**Table 1. Clinical Profile of Malignant and Serotonin Syndromes.**

	Malignant syndrome (n=16)	Serotonin syndrome (n=2)
Age [mean, range (years)]	65 (29-88)	38 (26-50)
Sex, M/F	8/8	1/1
Back ground diseases		
Depression	5	2
Dementia or parkinsonism	11	0
Clinical features		
Hyperthermia (at least 37.5°C)	16/16	1/2
Tachycardia	10/16	2/2
Hypertension	8/16	2/2
Hyperhidrosis	7/16	1/2
Sialorrhea	2/16	2/2
Mental status change or altered consciousness	8/16	1/2
Dysphagia	12/16	1/2
Muscle rigidity	16/16	2/2
Myoclonus	5/16	2/2
Tremor	4/16	2/2
Serum CK level [mean, range (U/L)]		
First examination	2,709 (461-10,065)	129 (57-201)
Maximum	3,947 (506-10,084)	444 (201-687)

CK: Creatine kinase

**Table 2. Number of Patients Fulfilling Diagnostic Criteria.**

Reference number	Malignant syndrome criteria			Serotonin syndrome criteria	
	[4]	[5]	[6]	[7]	[8]
Malignant syndrome	16/16	Definite 8/16 Probable 3/16	5/16*	3/16	3/16
Serotonin syndrome	1/2	1/2	1/2	1/2**	2/2**

Note: \*Two of the 11 patients who did not fulfil Caroff's criteria fulfilled 4 of 5 items of this criteria. Only one item as 'treatment with neuroleptics' was not fulfilled. \*\*One of 2 patients with SS was treated with atypical psychiatric. However, the dosage of this agent was not started or increased; thus, these criteria were fulfilled.

and 28,700. Markedly elevated CK levels and WBC counts generally strongly suggest MS; however, we could not exclude SS in one patient with DLB who had a mildly elevated CK level of 783. Both patients with SS fulfilled the criteria of Birnes; however, they did not fulfill the criteria of Sternbach because one of the two patients also received atypical antipsychotics. One of the patients with SS who was treated with serotonergic agents and atypical antipsychotics fulfilled all three MS criteria. However, the obvious signs of myoclonus, tremor, and hyperhidrosis with normal CK levels (57 U/L) at admission suggested SS rather than MS. One patient with MS who had PD and who was treated with an MAO-B inhibitor (having serotonergic effects) did not fulfill two of the SS criteria.

### Treatments and prognosis

Of the 16 patients with MS, 11 were treated with dantrolene and 11 were treated with bromocriptine. The drug dosages were tapered after the symptoms of MS and SS became well controlled. Both patients with SS received cyproheptadine (12 mg/day). One patient with SS in whom distinguishing SS from MS in the acute phase was difficult also

received dantrolene. Furthermore, five patients with MS in whom distinguishing MS from SS was difficult received cyproheptadine. Of the 16 patients with MS, one died because of disseminated intravascular coagulation and acute renal failure that required continuous renal replacement therapy, one was restricted to a wheel chair, four could walk with assistance, and ten could independently ambulate. Both patients with SS demonstrated disease progression after their first examination, but they recovered after cyproheptadine therapy and were able to walk at discharge.

## Discussion

This study revealed two important clinical findings. First, there was a difference in the frequency of MS and SS in the general hospital setting. MS appeared to occur in patients with dementia or parkinsonism rather than in those with psychiatric conditions in our general hospital setting. Moreover, the frequency of MS was much higher than that of SS. Second, there is a frequent difficulty in the differential diagnosis of MS and SS. A contributing factor could be that the diagnostic sensitivities differ greatly for the different diag-

nostic criteria.

Estimates for the incidence of MS have ranged from 0.02% to 12.2% in all patients exposed to neuroleptics (9), and meta-analyses have demonstrated that of 141,291 cases from 26 prospective and retrospective studies, 140 (0.1%) had neuroleptic MS (10). Conversely, the incidence of SS remains unknown because many cases are unrecognized and/or are not reported (11). Differences in the frequency, severity, and prognosis of MS and SS may arise from those in the frequency of receiving psychiatric medication, awareness levels of these syndromes, and early treatment initiation. Serotonergic drugs such as SSRIs and SNRIs are increasingly used for treating patients with depression; consequently, an increased incidence of SS should thus be expected (12). However, our study clearly revealed a lower frequency of SS than of MS. In our study, the underlying etiologies, such as dementia and parkinsonism were more common than psychiatric disorders in patients with MS. Elderly patients with parkinsonism and dementia often have psychiatric or behavioral problems; treating these patients with psychiatric agents increases their risk for developing MS. In addition, MS in patients with parkinsonism can occur without treatment with neuroleptic drugs or the withdrawal of anti-parkinsonism drugs [3]. Typical neuroleptic medications cannot be used for suppressing hallucination or psychosis in patients with PD because extrapyramidal side effects tend to worsen parkinsonian motor control, whereas atypical neuroleptic medications decrease D2 receptor affinity to a level lower than that of typical neuroleptics and appear to be effective in suppressing hallucinations in patients with PD (13). However, atypical neuroleptics can also act as causative agents of MS (14), as demonstrated in our study.

Our study also demonstrated that the differential diagnosis of MS and SS is often difficult for the following two reasons: (1) clinically, MS and SS have similar signs and symptoms and (2) patients are frequently treated with both neuroleptics and serotonergic agents, as were the patients in our study. Pharmacokinetic factors may play a role in MS because SSRIs can increase plasma anti-psychotic concentrations. Thus, the use of SSRIs may be associated with an increased risk for MS development in patients receiving antipsychotics (15), a factor that makes an accurate differential diagnosis difficult. Moreover, in patients with PD, MAO-B inhibitor treatment can make diagnosing MS or SS difficult because MAO-B inhibitors also cause SS. Some clinical aspects may aid in differentiating the two syndromes; for example, myoclonus is rare in MS, but common in SS and leucocytosis is rare in SS but common in MS (16). However, our study demonstrated that elevated WBC counts were observed in the two patients with SS and in at least two patients with MS (presenting with myoclonus) who did not receive serotonergic drugs. This finding indicates that myoclonus is not an exclusive sign of MS. In our study, the most difficult patient to diagnose was the one with DLB (presenting with myoclonus), who was initially diagnosed as having MS with a mildly elevated CK level (783 IU/L). Be-

cause this patient fulfilled the MS and SS criteria and received drugs that induced both MS and SS, we could not exclude SS, thus resulting in us suspecting an overlapping syndrome or some otherwise unclassified syndromes. Some researchers consider overlapping syndromes to exist on a spectrum of the same disorder (e.g., the overlapping syndrome of MS and SS) (2, 17, 18). A retrospective study showed that 65% of patients with reported olanzapine-induced MS concurrently exhibited SS features, according to the SS criteria of Sternbach (17). Regarding the diagnostic criteria, one meta-analysis showed that the reported incidence of MS varied greatly because of the different diagnostic criteria employed (10). Simple criteria, such as those of Levenson may lead to an overdiagnosis; other conditions, such as SS easily fulfill such simple criteria. In contrast, the use of stringent criteria may result in the underdiagnosis of mild cases of MS or MS in its early stages. In our opinion, a two-step approach for these two syndromes may be better. First, simple diagnostic criteria that include both SS and MS (e.g., fever, altered mentation/consciousness disturbance, autonomic symptoms, and motor symptoms) are required for early detection. Second, a scoring system or criteria for differentiating these two syndromes should then be used.

One limitation associated with the present study was the hospital setting. A considerable number of patients with MS or SS might be admitted to psychiatric hospitals where they are treated with psychiatric medications. In our city, there are two psychiatric hospitals, which had inpatient beds. The exact number of MS and SS patients in the same period in our region who were not admitted in our hospitals was therefore unclear.

In conclusion, in our study, the occurrence of MS was found to be much higher than that of SS. Underlying etiologies, such as dementia and PD were more common than psychiatric disorders in patients with MS in general hospital settings. Because overlapping of signs and symptoms occurs in MS and SS, patients are treated with both psychiatric and serotonergic drugs, making distinguishing between the two syndromes difficult. As a result, the establishment of new diagnostic criteria that particularly focus on distinguishing MS from SS is therefore required.

**The authors state that they have no Conflict of Interest (COI).**

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