Points of Intersection Between Mental Disorder and the Autonomic Nervous System, and Their Characteristics

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The responses of the body to physical and psychological stress can be broadly classified into: physiological responses mediated by the autonomic nervous system; responses mediated by the neuroendocrine system, including the hypothalamus–pituitary–adrenal axis or neuropeptides; changes in the immune system, which correlate with the autonomic nervous system and neuroendocrine system; and emotional or behavioral changes. Acute responses to stress stimuli result from activation of the sympathetic nervous system. Chronic stress is also believed to exacerbate the condition of patients with diseases which are regarded as psychosomatic disorders in Japan.

A concept similar to psychosomatic disorder that has been proposed in recent years is functional somatic syndromes. It is common for mental disorders to be accompanied by complaints of physical suffering. The term “autonomic nervous disorder” has been widely used for patients with these complaints. Symptomatological classifications are mainly used nowadays, and in the field of psychiatry this disorder is diagnosed as a somatoform disorder. In the DSM-5, this is referred to as Somatic Symptom and Related Disorders, broadly classified into somatic symptoms and conversion disorder. Patients with depression often complain of autonomic symptoms. We give an outline about these diseases.

Key words: autonomic symptoms, somatoform disorder, depression

Introduction

The responses of the body to physical and psychological stress can be broadly classified into: physiological responses mediated by the autonomic nervous system; responses mediated by the neuroendocrine system, including the hypothalamus–pituitary–adrenal (HPA) axis or neuropeptides; changes in the immune system, which correlate with the autonomic nervous system and neuroendocrine system; and emotional or behavioral changes such as anxiety or loss of appetite.

In contrast to the somatic nervous system, which is the body’s system of voluntary nerve control, the autonomic nervous system controls involuntary functions such as circulation, respiration, digestion, perspiration and thermoregulation, endocrine function, reproductive function, and metabolism. The autonomic nervous system comprises the sympathetic and parasympathetic nervous systems, and a single organ will often be supplied with nerves from both. The two systems generally act in an antagonistic manner on a given organ. Acute responses to stress stimuli mainly result from activation of the sympathetic nervous system, and such responses include cessation of stomach movement, decreased...
secretion of digestive fluids, elevated heart rate and blood pressure caused by constriction of blood vessels, increased blood sugar level, and dilation of the pupils. These responses, referred to as emergency responses, are beneficial from the perspective of readying the body for fight or flight.  

Numerous reports have found that these physiological responses have an effect on physical disorders. Research suggests that catecholamine released as a result of stimulation of the sympathetic nervous system can lead to myocardial infarction, and triggers for this include waking up, Mondays, physical exertion, emotional upset, lack of sleep, cocaine, marijuana, anger, and sexual activity. Natural disasters, such as earthquakes or blizzards, and war are also associated with increases in new cardiac events. In Japan, increases in the death rate and the incidence of sudden death among cardiovascular disease patients following the Great Hanshin-Awaji Earthquake and Great East Japan Earthquake have been reported, and similar reports have been seen with disasters overseas.  

In addition, acute physical stress such as head injury or acute cerebrovascular disease can result in hemorrhagic gastric ulcer or “takotsubo” cardiomyopathy (apical ballooning). The latter is an acute, reversible left ventricular dysfunction brought on by emotional or physical stress, presenting with symptoms of serious chest pain, acute dyspnea, reduced blood pressure, and, sometimes, cardiogenic shock. The electrocardiogram of takotsubo cardiomyopathy shows changes such as T-wave inversion and ST-segment elevation suggestive of acute coronary infarction. The prognosis is generally considered favorable, but the condition may recur in some individuals and can prove fatal. In addition to acute psychomotor agitation, takotsubo cardiomyopathy is reportedly associated with acute alcohol withdrawal, limbic encephalitis, and electroconvulsive therapy (ECT), suggesting a relationship with catecholamines. Chronic stress in animal models has also been shown to cause pathological changes in the cardiovascular system, arising from inflammatory changes due to oxidative imbalances. Autonomic and emotional responses may, on the other hand, be moderated by the ventro-medial prefrontal cortex (vmPFC) via the parasympathetic nerves.  

Stress is also believed to exacerbate the condition of patients with hypertension, bronchial asthma, stomach ulcers, duodenal ulcers, irritable bowel syndrome, and functional dyspepsia, all of which are regarded as psychosomatic disorders in Japan. The concept of psychosomatic disorder was originally proposed by Franz Alexander at the beginning of the 20th Century, but the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) do not include this as a pathological entity. The FSS concept does not question the involvement of psychosocial factors in the original onset of the

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Functional somatic syndromes by specialty</th>
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<tbody>
<tr>
<td>Gastroenterology</td>
<td>Irritable bowel syndrome, non-ulcer dyspepsia</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>Premenstrual syndrome, chronic pelvic pain</td>
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<tr>
<td>Rheumatology</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Atypical or non-cardiac chest pain</td>
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<tr>
<td>Respiratory medicine</td>
<td>Hyperventilation syndrome</td>
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<tr>
<td>Infectious diseases</td>
<td>Chronic (postviral) fatigue syndrome</td>
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<tr>
<td>Neurology</td>
<td>Tension headache</td>
</tr>
<tr>
<td>Dentistry</td>
<td>Temporomandibular joint dysfunction, atypical facial pain</td>
</tr>
<tr>
<td>Ear, nose, and throat</td>
<td>Globus syndrome</td>
</tr>
<tr>
<td>Allergy</td>
<td>Multiple chemical sensitivity</td>
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disease, but maintains that somatic disorders that are hard to explain with conventional medical models give rise to factors such as feelings of anxiety or depression and maladjustment, which can amplify or prolong the somatic disorder.

Somatic symptoms in mental disorder

It is extremely common for mental disorders to be accompanied by complaints of physical suffering. The specific physical disorders are wide-ranging and include headache or heavy head, dizziness, tinnitus, heart palpitations, dyspnea, stomach discomfort, pain, chills, and numbness. For this reason, many patients are first examined at a general medical clinic or department for somatic symptoms. A study at Jichi Medical University found that among 1,194 patients who first visited the general internal medicine outpatient department, 148 (12.4%) were diagnosed as presenting with mental disorder, of whom 19.6% exhibited depression, 14.9% anxiety disorder, and 14.2% somatization disorder. Cases have also been described of patients visiting a department for somatic disorder and, when no abnormality is found, subsequently visiting a different doctor where the same thing happens and the cycle repeats itself. Considerable impediments to everyday life may be involved, and appropriate responses are needed.

The term “autonomic nervous disorder” has been widely used for some time for patients with these complaints. Research into autonomic nervous disorder has been carried out for a long time and is described in a classic work from the end of the 19th Century. The circadian rhythm involves a complex mechanism of mutual influence and control among the autonomic nerve center of the hypothalamus in the diencephalon, the peripheral sympathetic and parasympathetic nerves, and the cerebral cortex, limbic system, brainstem, spinal cord, and other nervous systems. Autonomic nervous disorder occurs if some functional or organic disorder of this mechanism arises. The notion that the cause of functional abnormality was to be found in the vagus nerve led to the use in the past of names such as Neurrose des Vagus (Rosenbach, 1878), hysterische Vagusneurose (Noorden, 1891), and chronische Vagusneurose (Quelzer, 1908). The disorder has also been classified into types such as circulatory (cardiac, vascular) neurosis, neurocirculatory asthenia, gastrointestinal neurosis, respiratory neurosis, bladder neurosis, skin neurosis, and genital neurosis, depending on the sites of symptoms. A great number of internal and external factors are involved in determining the site of symptoms, including heredity and predisposition, biorhythms, addiction (alcohol, tobacco, narcotics, and other stimulants), social background (family, workplace, school, relationships, etc.) and environmental factors such as climate and natural features.

Symptomatological classifications are mainly used nowadays, and in the field of psychiatry this disorder is diagnosed as a somatoform disorder. In the DSM-5, this is referred to as Somatic Symptom and Related Disorders, broadly classified into somatic symptoms and conversion disorder.

1. Somatic symptom and related disorders

Table 2: Somatic symptom disorder (DSM-5)

<table>
<thead>
<tr>
<th>A.</th>
<th>One or more somatic symptoms that are distressing or result in significant disruption of daily life</th>
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<tbody>
<tr>
<td>B.</td>
<td>Excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of following:</td>
</tr>
<tr>
<td>1.</td>
<td>Disproportionate and persistent thoughts about the seriousness of one’s symptoms</td>
</tr>
<tr>
<td>2.</td>
<td>Persistently high level of anxiety about health or symptoms</td>
</tr>
<tr>
<td>3.</td>
<td>Excessive time and energy devoted to these symptoms or health concerns</td>
</tr>
<tr>
<td>C.</td>
<td>Although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically more than 6 months)</td>
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(American Psychiatric Association: Desk reference to the diagnostic criteria from DSM-5, 2013)
Somatization needs to be addressed through appropriate use of pharmacotherapy with antidepressants or atypical antipsychotic drugs, ECT, and psychotherapy such as cognitive-behavioral therapy. Previous editions of the DSM had a diagnostic classification of pain disorder. In the DSM-5, conditions classified as somatic symptom disorder in which pain is the main somatic symptom now come under the sub-classification of “somatic symptom disorder with predominant pain”.

When individuals face problems in family life or at school or the workplace, and these problems become psychosocial stress leading to unpleasant emotions (alienation, lack of personal trust, sense of loss, feelings of guilt, inferiority complex, self-denial, etc.), this stress is commonly released through overeating, drinking, or smoking. Where psychosocial stress is present, the sympathetic nervous system is activated and visceral pain such as abdominal or chest pain can readily develop. In addition, increased mobility as a result of overadaptation can lead to musculoskeletal pain. Furthermore, chronic stress appears capable of leading to decreases in neurotransmitters such as serotonin and noradrenaline in the synaptic cleft, causing hypoactivity of the descending pain inhibitory system and thus resulting in hyperalgesia. To add to this, unpleasant emotional experiences activate the insular cortex, anterior cingulate cortex, and amygdala, further increasing the discomfort of organic and functional pain. Emotions such as anxiety and tension reportedly lead to localized decreases in blood flow accompanied by deterioration in muscle tone and sympathetic hyperactivity, causing aggravation of symptoms. One study that found that patients diagnosed with MPS have a notably high tendency towards neurosis on the Cornell Medical Index (CMI) and Minnesota Multiphasic Personality Inventory (MMPI). MPS thus appears to have a strong association with psychological factors.

### 2) Conversion disorder (functional neurological symptom disorder) (Table-3)

The symptoms of conversion disorder include exhaustion or paralysis, abnormal movement (trembling, dystonia, myoclonus, gait disturbance, etc.), swallowing symptoms, speech symptoms (aphonia, poor articulation, etc.), spasms or convulsions, stupor or sensory loss, and specific sensory symptoms of vision, olfaction, and hearing. Conversion disorder is more prevalent among women, with a male: female ratio between 1:2 and 1:10, and also tends to be more prevalent among people of low educational level and low income. This disorder often coexists with dissociative disorder and major depressive disorder, as well as histrionic, antisocial, borderline, and dependent personality disorders.

When examining cases of conversion disorder, scientific objective findings require interpretation in an appropriate fashion. Also, one study in the field of neuroimaging research found that when a patient with conversion disorder paralysis tried to move her paralyzed leg, no activity was apparent in the primary association area, but activity was identifiable in the orbitofrontal area and anterior cingulate gyrus. In another study, activity was only decreased in the dorsolateral prefrontal cortex of...
the paralyzed side. Increases in knowledge relating to the neural basis and associativity of conversion disorder are expected.

2. Depression
Patients with depression, particularly the elderly, often complain of autonomic symptoms including localized pain such as headache, lower back pain, or sore tongue; gastrointestinal symptoms such as stomach discomfort or loss of appetite; symptoms related to excretion, such as incomplete bowel movements or frequent urination; and tinnitus, dizziness, lightheadedness, and numbness of the limbs. Depression in which the main symptoms are autonomic, such as loss of appetite, insomnia, weight loss, impotence, and menstrual irregularity, but without conspicuous depressed mood or inhibition, is known as masked depression.

Numerous reports have described autonomic nervous system abnormalities in depression, including a negative correlation between the Beck Depression Inventory score and heart rate recovery, and acute myocardial infarction patients have a three-fold higher risk of depression, while depressive symptoms increase the risk of cardiovascular events. The literature on the relationship between depression and cardiovascular disorder is extensive, and even the finding that depression increases the mortality rate of coronary disease has been reported.

The mechanism of the autonomic nerves symptom in patients with depression is not understood clearly. We mentioned the response of autonomic nervous system and immune system at the stress load above. The principal autonomic neurotransmitters, acetylcholine and noradrenaline, are involved in immune regulation in the context of inflammation through various molecular pathways. The dysfunction of the HPA axis in patients with depression is known widely for a long time. FK506-binding protein 51 (FKBP5) plays an important role in the negative feedback regulation of the HPA axis. The C/T single nucleotide polymorphism in the intron 2 of the FKBP5 gene affects cortisol secretion, and has been implicated in the pathophysiology of depression.

The autonomic nervous system strongly catches the effect of the circadian rhythm mainly on melatonin and the orexin. Decreased of orexin-A levels were reported in the CSF of suicidal patients with major depressive disorder. Daylight regulates suprachiasmatic nucleus (SCN) circadian organization and its control of melatonin secretion in mammals. As a result of long winter nights, delayed morning offset of nocturnal melatonin secretion could be the main cause for winter depression. Bright light and sleep restriction are antidepressant and sometimes trigger mania. We thought that these findings were associated with the autonomic nerves symptom of patients with depression.

Cases in which patients exhibit psychiatric symptoms resembling depression as a result of physical disease or drugs have also been described. In particular, depression is readily exhibited with diseases such as cerebrovascular disease, neurodegenerative disease, endocrine disorder, autoimmune disorder, and malignant tumor. Once a diagnosis of depression has been made, an approach is needed that takes into account the fact that complications of physical disease may develop during the course of the disease.

The length of an untreated episode of depression is reportedly negatively correlated with the rate of improvement in scales of depression and somatic symptoms, indicating the pressing need to distinguish depression as soon as possible.

References