

# Clinical Manifestations of Neuropsychiatric Disorders

Koho Miyoshi and Yasushi Morimura

**Abstract** Cerebral disorders commonly cause psychiatric symptoms. It is recommended to call psychiatric symptoms or syndromes that are caused by organic cerebral disorders “neuropsychiatric symptoms” or “neuropsychiatric syndromes.” And, in this context, cerebral disorders, which cause psychiatric symptoms, are called neuropsychiatric disorders. The main characteristics of neuropsychiatric symptoms are (1) concurrent occurrence of the various psychiatric symptoms, (2) cognitive impairment as a core symptom, (3) the possibility of early cerebral symptoms, and (4) occasional resemblance to endogenous psychiatric disorders. The characteristics of neuropsychiatric symptoms, namely, anxiety, neurotic complaint, apathy, mood disorder, hallucinations, delusions, behavioral and personality changes, delirium, and cognitive impairment (dementia), are discussed briefly.

**Keywords** Cognitive impairment • Dementia • Neuropsychiatric disorders • Neuropsychiatry • Organic psychosis

## Introduction

Almost all brain disorders may cause psychiatric symptoms [1]. Psychiatric symptoms caused by organic brain disorders could be called “neuropsychiatric” symptoms. Psychiatric manifestations caused by organic brain disease have been traditionally called organic mental disorders. In DSM-IV-TR, however, the term “organic psychosis” is not applied to the psychosis caused by organic cerebral disorders. Because the “organic” or neurobiological bases of psychoses, including

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endogenous psychiatric disorders, have been revealed by recent investigations, it would be recommended not to use the poorly defined term “organic” to avoid implying that mental disorders other than “organic” mental disorders do not have a neurobiological component. Alternatively, the use of the term “neuropsychiatric symptoms” would be recommended to indicate psychiatric symptoms caused by organic cerebral disorders. In this context, organic cerebral disorders or neurological disorders that cause psychiatric symptoms could be called “neuropsychiatric disorders.”

Neuropsychiatric disorder commonly occurs in elderly patients and occasionally mimics endogenous psychoses. Therefore, the organic factors should be carefully evaluated in diagnostic procedures in patients with psychiatric symptoms among the elderly. The clinical manifestations and characteristics of neuropsychiatric symptoms, especially in elderly patients, are briefly discussed in this chapter.

## **Neuropsychiatric Symptoms and Neuropsychiatric Disorders**

Neuropsychiatric symptoms could be defined as psychiatric manifestations of cerebral (neuropsychiatric) disorders. Cerebral disorders cause various psychiatric symptoms.

Some of these symptoms occasionally mimic the psychiatric manifestation of endogenous psychiatric disorders. In ICD-10 [2], psychiatric symptoms caused by organic cerebral disorders are classified as organic (including symptomatic) mental disorders. The psychiatric symptoms described in this classification are as follows: dementia in Alzheimer’s disease, vascular dementia, dementia in other diseases classified elsewhere, unspecific dementia, organic amnestic syndrome, not induced by alcohol and other psychoactive substances, other mental disorders caused by brain damage and dysfunction and by physical illness, including organic hallucinosis, organic catatonic disorder, organic delusional disorder, organic mood disorder, organic anxiety disorder, organic dissociative disorder, organic emotionally labile disorder, mild cognitive disorder, other specific mental disorders, and personality and behavioral disorders resulting from brain disease, damage, and dysfunction.

In the core curriculum of the International Neuropsychiatric Association, neuropsychiatric symptoms and syndromes are also classified as follows: cognitive disorders (dementias and predementia syndromes, nondementing cognitive disorders), seizure disorders, movement disorders, traumatic brain injury, secondary psychiatric disorders (psychosis, depression, mania and anxiety disorders secondary to “organic” brain disease), substance-induced psychiatric disorders, attentional disorders, and sleep disorders.

The core curriculum of the American Neuropsychiatric Association also defines the major neuropsychiatric syndromes as delirium, the dementias, and the major primary psychiatric disorders, including those of learning and communication, and motor skill disorders. Also, neuropsychiatric disorders are defined as neurological disorders with cognitive, emotional, behavioral features; neurodegenerative disorders

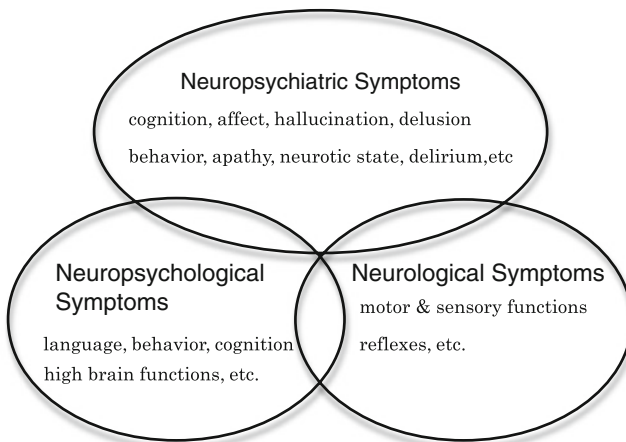
(dementias), movement disorders, stroke, epilepsy, multiple sclerosis, traumatic brain injury, infections, neuroendocrine disorders, metabolic disorders, intoxication, etc. [3].

The term “neuropsychiatric disorders” should be applied to brain diseases that cause psychiatric symptoms. Therefore, organic cerebral disorders, including neurodegenerative diseases (Alzheimer’s disease, frontotemporal lobar degeneration, progressive supranuclear palsy, corticobasal degeneration, Huntington’s disease, and Lewy body disease), Creutzfeldt–Jakob disease, cerebrovascular disorders, subdural hematoma, encephalitis, traumatic brain injury, brain tumor, metabolic encephalopathy, intoxication, and normal pressure hydrocephalus, could be called neuropsychiatric disorders.

## Characteristics of Clinical Manifestations of Neuropsychiatric Disorders

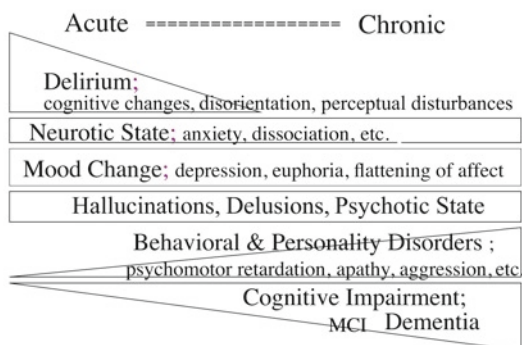
### *Multiple Neuropsychiatric Symptoms Occur Simultaneously*

Brain diseases commonly cause neurological, neuropsychological, and psychiatric symptoms concurrently in the course of illness (Fig. 1). Therefore, clinical manifestations of the cerebral disorders usually are composed of these three components. Neurological symptoms, such as motor and sensory disturbances, are commonly encountered in neurological disorders. Neuropsychological symptoms, such as aphasia, apraxia, and agnosia, caused by the circumscribed lesion of the cerebrum, commonly occur in cerebral disorders. Also, diffuse lesions of the cerebrum usually cause neuropsychiatric symptoms such as cognitive impairment, mood disorder,



**Fig. 1** Structures of the clinical manifestations of cerebral disorders

### Structures of Neuropsychiatric Symptoms



**Fig. 2** Structures of the neuropsychiatric symptoms of cerebral disorders

apathy, hallucination, delusion, and behavioral disorders. These three components form complex clinical manifestations of neuropsychiatric disorders.

Multiple neuropsychiatric symptoms, such as cognitive impairment, disturbance of consciousness, anxiety, mood disorders, hallucination, delusion, behavioral change, and apathy, commonly occur concurrently in the course of cerebral disorders (Fig. 2). The psychiatric symptoms are usually accompanied by other psychiatric symptoms. Namely, depression, neurotic states, behavioral changes, apathy, and cognitive impairment occur simultaneously in Alzheimer's disease, and mood change, apathy, visual hallucination, and cognitive impairment are encountered concurrently in patients with Parkinson's disease. Any of the neuropsychiatric symptoms rarely occur independently in the course of illness. Clinical manifestations of neuropsychiatric disorders usually consist of the multiple components of psychiatric symptoms.

### ***Probable and Possible Symptoms of Neuropsychiatric Disorders***

Cognitive impairment is a core symptom of neuropsychiatric disorders. Almost all neuropsychiatric symptoms are intermingled with impairment of cognition, if evaluated carefully. If distinct cognitive impairment is evaluated in psychiatric patients, it could be a sign indicating the symptoms might be caused by cerebral disease.

Disturbance of consciousness, on the other hand, could be a clue for diagnosis of cerebral disorders, if the possibility of physical illness can be ruled out. In the diagnostic procedure, these two symptoms, namely, cognitive impairment and disturbance of consciousness, indicate that the psychiatric symptoms are probably caused by brain disease. Therefore, these symptoms could be called "probable" neuropsychiatric symptoms (Fig. 3).

### Probable and Possible Neuropsychiatric Symptoms

1. Probable Neuropsychiatric Symptoms
  - Cognitive impairment
  - Disturbance of consciousness
  
2. Possible Neuropsychiatric Symptoms
  - Neurotic complaints, anxiety
  - Mood changes
  - Psychotic States: Hallucination & delusion
  - Behavioral and personality changes

**Fig. 3** Probable and possible neuropsychiatric symptoms

On the other hand, psychiatric symptoms such as neurotic complaints, mood changes, hallucination, delusion, and behavioral and personality changes could possibly be caused by cerebral disorders. Therefore, these symptoms could be called “possible” neuropsychiatric symptoms (Fig. 3).

### ***Neuropsychiatric Symptoms Could Be the Earliest Symptoms in Cerebral Disorders***

Mild neuropsychiatric symptoms, such as anxiety, depression, apathy, and personality changes, occasionally precede dementia in cerebral disorders (Fig. 4). Mild psychiatric symptoms could be the earliest manifestations of the neuropsychiatric disorders. Occasionally these symptoms are composed of vague somatic complaints. Patients with neuropsychiatric disorders commonly complain of subjective work difficulties, forgetting the location of objects, decreased functioning in demanding employment settings, and difficulty in traveling to new locations in the early stage of their illness. Hypochondria, anxiety, irritability, dysphoria, dysthymia, depressive mood, agitation, euphoria, hypomanic mood, flattening of affects, sleep disorder, apathy, and psychomotor retardation may occur, preceding dementia, in the initial stage of brain disease.

#### Mild Neuropsychiatric Symptoms, precede Dementia

- 1) Neurotic Symptoms: Headache, vertigo, dizziness, fatigueability, listlessness, pain, weakness, hypochondria, anxiety, irritability,
  
- 2) Mood Disorders: dysphoria, dysthymia, depressive mood, agitation, euphoria, hypomanic mood, flattening of affect, sleep disorders,
  
- 3) Behaviors: apathy, psychomotor retardation, subjective work difficulties,
  
- 4) Cognitive Impairment: forgetting location of objects, decreased functioning in demanding employment settings, and difficulty in traveling to new locations.

**Fig. 4** Mild neuropsychiatric symptoms that precede dementia

Cognitive impairment preceding dementia is called mild cognitive impairment (MCI) [4]. It is reported that MCI is commonly accompanied by neuropsychiatric symptoms such as depression, dysphoria, apathy, irritability, anxiety, agitation, aberrant motor behavior, and parkinsonian-like signs. Neuropsychiatric symptoms in the MCI stage could be the predictors of conversion to dementia [5].

### ***Neuropsychiatric Symptoms Are Not Pathognomonic to a Certain Cerebral Disorder***

Psychiatric symptoms are nonspecific to certain neurological diseases. Therefore, it usually is not possible to indicate what kind of disease causes the psychiatric symptoms in the patients. Almost all neuropsychiatric symptoms may occur in any of the cerebral disorders. For example, depressive mood and agitation occasionally occur in Alzheimer's disease, cerebrovascular disorders, and Parkinson's disease. Neurotic symptoms are commonly encountered in patients with Alzheimer's disease, traumatic brain injury, and seizure disorders, which means that no type of neuropsychiatric symptom is pathognomonic to a specific cerebral disorder.

### ***Neuropsychiatric Symptoms May Mimic Endogenous Psychoses***

Cerebral disorders may mimic endogenous psychoses. Paranoid-hallucinatory state and mood disorders could be caused by cerebral diseases. Visual hallucination, especially, commonly occurs in cerebral disorders. Delusions of persecution and infidelity are occasionally seen in patients with organic brain disorders. Less frequently, delusional misidentification occurs in neuropsychiatric disorders. Therefore, endogenous psychosis should be diagnosed carefully by excluding the possibility of cerebral disorders.

The neurobiological basis of the endogenous psychoses, such as schizophrenia and mood disorder, is still unknown. However, the pathophysiology of the endogenous psychoses could be revealed by neurobiological investigations of neuropsychiatric disorders in the future.

## **Neuropsychiatric Symptoms and Syndromes**

Various neuropsychiatric symptoms and syndromes, such as anxiety, neurotic complaints, apathy, mood disorder, hallucination, delusion, behavioral change, personality alteration, and delirium, occur in patients with cerebral disorders and cause dementia in the advanced stages of illness (Fig. 5).

Diseases	MCI Type	Disturbance of Cognitive Functions	Mood Disorders	Volition	Neurotic State	Other Non-cognitive Symptoms	Other Neuropsychiatric Symptoms
Vascular Cognitive Impairment	Multiple or Nonmemory Domains MCI	Executive Function	Depression Emotional Incontinence	Apathy	Somatic complaints Anxiety	Personality Change	Delirium Neurological Signs
Alzheimer's Disease	Amnesic MCI	Memory	Depression Depressive Pseudo-dementia	Apathy	Somatic complaints Anxiety	Personality Change Delusion	
Frontotemporal Dementia	Nonmemory Domains MCI	Language Executive Function	Depression Hyperthymia	Apathy		Personality Change	
Parkinson's Disease	Nonmemory Domains MCI	Subcortical Dementia PDD (DLB)	Depression	Apathy Bradyphrenia	Somatic Complaints Anxiety		Parkinsonism
Dementia with Lewy Bodies	Memory Domains MCI	Memory or Nonmemory	Depression	Apathy		Visual Hallucination, Delusion	Delirium, Parkinsonism
Progressive Supranuclear Palsy	Nonmemory Domains MCI	Subcortical Dementia	Depression	Apathy		Personality Change	Nuchal Rigidity Stiffness

**Fig. 5** Neuropsychiatric symptoms in cerebral disorders

## ***Anxiety and Neurotic Complaints***

Anxiety commonly occurs in the initial stage of a neuropsychiatric disorder [6, 7]. However, it usually becomes less obvious as the progress of cognitive decline continues. Anxiety, intermingled with depressive mood or dysphoria, is one of the most common neuropsychiatric symptoms in Alzheimer's disease and vascular dementia. Somatic distress, such as headache, vertigo, dizziness, fatigability, listlessness, and feeling of weakness are occasional complaints. Excessive anxiety is usually accompanied by restlessness, irritability, muscle tension, fears, and respiratory symptoms of anxiety.

## ***Apathy***

Apathy, a syndrome of decreased initiation and motivation, is a common neuropsychiatric symptom in demented patients. The prevalence of apathy is reported to be almost 65% of patients with dementia and 70% in Alzheimer's disease patients. Although there is some overlap between apathy and depression, these two conditions are independent in the course of illness [8]. Apathy is significantly associated with more severe cognitive deficit and has been reported to reflect the interaction between cholinergic deficiency and neuropathological changes in the frontal brain regions. Increased apathy is associated with poor quality of life.

## ***Mood Disorder***

The prevalence of depression in cerebral diseases is strikingly high, particularly in Alzheimer's disease, Parkinson's disease, and cerebral stroke. Depression is one of the most common neuropsychiatric symptoms in patients with Alzheimer's disease. Depressive symptoms that most strongly discriminate between Alzheimer's disease patients with (major depression) and without (minor depression) sad moods are guilty ideation, suicidal ideation, loss of energy, insomnia, weight loss, psychomotor retardation /agitation, poor concentration, and loss of interest [8].

Patients with Alzheimer's disease are more likely to report a diminished ability to concentrate or indecisiveness and are less likely to experience sleep disturbances and feelings of worthlessness or excessive guilt during their major depressive episodes [9]. Among the various neuropsychiatric symptoms, depression frequently occurs in the preclinical phase of Alzheimer's disease and is considered to be one of the predictors of conversion to dementia in the stage of MCI [5].

Depressive patients with Parkinson's disease develop depressive mood change, loss of interest, and feelings of hopelessness [10]. Diminished ability to concentrate is also seen in parkinsonian patients with depression. Psychiatric features of guilt,



self-reproach, or feelings of guilt and punishment are occasionally manifested in depression in Parkinson's disease. Anxiety, irritability, suicidal ideation, and depressive delusions are less frequent in Parkinson's patients with depression when compared to endogenous depressives. In addition, circadian rhythm of mood and manic state are exceptional. Somatic complaints such as fatigue, constipation, headache, insomnia, loss of appetite, dizziness, and abnormal sweating are frequent in patients with Parkinson's disease and depression.

The concept of vascular depression was proposed because of the comorbidity of depression and vascular disease [11]. Therefore, the diagnostic criteria for vascular depression require a major depression associated with evidence of confluent or diffuse vascular lesions in the subcortical regions seen on neuroimaging. Disruptions of the prefrontal systems or their modulating pathway are hypothesized to cause depressive mood in cerebrovascular disorders. Clinical symptoms of vascular depression are characterized by greater disability and higher risk for poorer outcomes, which may be related in part to executive dysfunction and consequent disability. Patients with late-life depression have significant impairment in executive functioning.

Poststroke depression (PSD) is a complication that occurs in patients with cerebral stroke. It has been reported that stroke in the left hemisphere causes depression more frequently than that in the right hemisphere [12]. Magnetic resonance imaging (MRI)-defined vascular depression is late-onset depression with mild infarction and rather intense white matter abnormalities in MRI [13].

### ***Hallucinations and Delusions***

Visual hallucination is usually one of the symptoms of delirium, caused by acute cerebral dysfunctions or physical illnesses. Hallucinosis could be caused by a localized brain lesion, especially in the brainstem or occipital lobe. Visual hallucination is the most common type of hallucinations in cerebral disorders. Organic hallucinations are frequently accompanied by illusions and delusional misidentifications. Delusional elaboration of hallucination also may occur in elderly patients. Charles Bonnet syndrome is nonorganic hallucination in the elderly, characterized by visual impairment, vivid visual hallucination, and illusion without any other psychotic symptoms. A special type of auditory hallucination, namely, musical hallucination, may occur in geriatric patients with auditory disturbance.

Psychiatric symptoms develop usually in the advanced stage of Parkinson's disease during long-term treatment with dopaminergic drugs. Recurrent episodes of visual hallucination and illusion are characteristic features of drug-induced psychiatric symptoms of Parkinson's disease. In approximately half the parkinsonian patients, hallucinations are accompanied by cognitive impairments [10].

Recently, visual hallucinations and delusions are considered to be characteristic clinical features of "dementia with Lewy bodies." Visual hallucination and other perceptual disorders, including misidentification syndrome and visual agnosia, are

common symptoms in this disorder. Characteristic delusions, such as Capgras syndrome and “phantom boarders,” occasionally occur in patients in their old age. Delusions of persecution, especially delusion of theft, are frequently encountered in the early stage of Alzheimer’s disease. Delusions caused by cerebral diseases are usually poorly systematized and are occasionally accompanied by confabulation.

### ***Behavioral and Personality Changes***

Behavioral and personality changes characterized by disturbances of mood, volition, and cognition could be caused by chronic brain disorders [14]. Agitation, psychomotor retardation, apathy, and stereotyped behavior are common types of behavioral changes in chronic neuropsychiatric disorders. Aggression, screaming, restlessness, wandering, culturally inappropriate behavior, sexual disinhibition, hoarding, cursing, and shadowing are common behavioral disturbances in patients with dementia. Current pharmacologic treatments or sociopsychological interventions may ameliorate behavioral symptoms significantly.

Personality change is characterized by significant alterations of habitual patterns of behavior. It is usually accompanied by impairment of cognition and volition and by change of mood in cerebral disorders. Irritability, apathy, and exaggerated emotionality are common behavioral changes in various neurological disorders. Personality disorder frequently occurs, especially in the advanced stages of neurodegenerative disorders or vascular dementia.

### ***Delirium***

Delirium is a psychiatric state that is characterized clinically by transient disturbances of consciousness and attention, perception, memory, thinking, psychomotor behavior, and emotion. Visual hallucination and disturbance of sleep–wake rhythms occur frequently [15]. Acute cerebral damage, physical illnesses, and withdrawal of psychoactive substances of abuse, including alcohol, cause delirium. Complete recovery could be expected if the causal disorders or dysfunction diminished. During recovery from delirium, mild neuropsychiatric symptoms, such as disturbance of memory and attention, may continue for a long period, even for several months.

### ***Persistent Cognitive Impairment (Dementia)***

Persistent cognitive impairment is a core symptom of cerebral disorders. Brain diseases, for the most part, cause cognitive decline in the advanced stage. Therefore, persistent cognitive impairment could be a clue for the diagnosis of cerebral disorders.

As well as impairment of memory, disturbances of attention, abstract thinking, judgment, calculation, language, and executive function are common clinical features of dementia.

### **Dementia of the Alzheimer Type**

Dementia in Alzheimer's disease is clinically characterized by amnesic syndrome and neuropsychological symptoms, including aphasia, apraxia, and agnosia. Impairment of episodic memory is one of the most important criteria for the diagnosis of Alzheimer's disease [16]. It is characterized clinically by slowly progressive impairment of cognitive functions, occasionally accompanied by disturbance of mood, behavior, and psychiatric symptoms, such as hallucination and delusion. The Mini-Mental State Examination reveals the disturbance of attention, impairment of recent memory, and disorientation in the earliest stage of Alzheimer's disease. Language abilities, such as naming and reading, are relatively spared until the advanced stages of the illness.

### **Neurodegenerative Dementias of Non-Alzheimer Type**

Personality changes and language disturbances with less marked memory impairment are the main characteristics of cortical dementia in frontotemporal dementia. The early clinical features of frontotemporal dementia are changes of character and social behavior rather than impairment of memory and intellect. With the progression of the disease, impairment of cognitive functions, including memory, becomes obvious and slowly increases in severity. Stereotyped speech with a prominent reduction of vocabulary is conspicuous in the advanced stage of illness. Semantic dementia, as well as progressive nonfluent aphasia, is the characteristic clinical symptom of this type of dementia. Frontotemporal dementia with motor neuron disease is clinically characterized by the complication with motor neuron disease.

Subcortical dementia in progressive supranuclear palsy, corticobasal degeneration, Parkinson's disease, and Huntington's disease are characterized by peculiar "forgetfulness," psychomotor retardation, and mood changes. Progression of cognitive impairment with visual disturbance is a characteristic clinical feature of Creutzfeldt–Jakob disease, which causes a diffuse cortical degeneration with accentuation of occipital change. Progressive supranuclear palsy is clinically characterized by dementia, supranuclear ophthalmoplegia, and pseudobulbar palsy. Clinical characteristics of "subcortical dementia," namely, forgetfulness with psychomotor retardation, difficulty with complex problem solving and concept formation, and a relative absence of "cortical" features, including aphasia, apraxia, and agnosia, was originally described in this disorder.

Corticobasal degeneration is characterized clinically by cognitive impairment, rigidity, clumsiness, and "alien limb" phenomena.

Clinical features of dementia with Lewy bodies (DLB) are characterized by persistent cognitive impairment with fluctuation, recurrent visual hallucination, and parkinsonism [17]. It is still obscure what kind of factor causes the fluctuations of cognitive impairment and disturbance of consciousness.

Recently, it has been thought that the “dementia in Parkinson’s disease (Parkinson disease dementia, PDD)” and DLB is essentially the same  $\alpha$ -synucleinopathy in the spectrum of Lewy body disease [17, 18].

### **Vascular Cognitive Impairment**

Cerebrovascular disorders may cause persistent cognitive impairment. After Alzheimer’s disease, vascular dementia is the second most common disorder in the dementias of the elderly [19, 20]. Multiinfarction, and diffuse degeneration of the subcortical white matter, are the two main characteristic neuropathologies. Because hippocampal formation and adjacent structures are usually spared at the early stage of multiple cerebral infarctions, impairment of recent memory is not conspicuous in vascular cognitive impairment or vascular dementia until the advanced stage of illness. Executive dysfunction is conspicuous in comparison to memory impairment in the early stage of vascular dementia. Delirium occasionally intermingles with cognitive impairment in vascular dementia.

### **Conclusions**

In general, almost all organic cerebral diseases cause psychiatric symptoms. Psychiatric symptoms caused by organic cerebral disorders are neuropsychiatric symptoms. Needless to say, neuropsychiatric symptoms and syndromes are the main target of neuropsychiatric studies. The main components of neuropsychiatric symptoms are cognitive impairment and disturbance of consciousness. Other neuropsychiatric symptoms, such as depression, anxiety, paranoid-hallucinatory states, and behavioral and personality changes, also commonly occur in the course of organic cerebral disorders. Mild neuropsychiatric symptoms could be the earliest manifestations of cerebral disorders. Cerebral diseases commonly cause neurological, neuropsychological, and psychiatric symptoms concurrently in the course of illness. Multiple neuropsychiatric symptoms commonly occur concurrently in the course of cerebral disorders. The organic factors should be carefully evaluated in the psychoses, especially in patients of older age. Clinicians who engage in the treatment of cerebral disorders or psychiatric disorders should have enough experience in the integrating neuroscience, that is, neuropsychiatry.

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