

## Review Article



# Clinical Aspects of Neurobehavioral Symptoms of Dementia

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## ABSTRACT

Neurobehavioral symptoms of dementia (NBSD) are very common and are significant symptoms of the illness, contributing most to caregiver burdens and often resulting in premature institutionalization of the person with dementia. The main symptoms of NBSD are anxiety, depression, delusions, and hallucinations. NBSD produce significant problems for both patients and caregivers. The pathophysiology of NBSD is determined by genetic, structural, or environmental factors. Therefore, treatment of NBSD requires continuous and organic cooperation between patients, caregivers, social environments, and doctors. Therefore, it is important for neurologists, who mainly view NBSD for dementia patients, to increase their understanding of these more comprehensive areas as well as the latest insights and treatments to help patients and caregivers.

**Keywords:** Dementia; Anxiety; Delusions; Depression; Hallucination

## INTRODUCTION

Dementia is a syndrome in which there is deterioration in cognitive function (i.e., the ability to process thought) affecting daily lives. Its patients suffer not only cognitive but also non-cognitive impairment. Symptoms caused by a non-cognitive impairment are personality change, delusions, hallucinations, mood disorders, sleep disorders, change in appetite, altered sexual behavior, and disturbed psychomotor activity. Neurobehavioral symptoms have been known to appear mostly during the onset of dementia.<sup>1</sup> Caregivers or families feel more overwhelmed by patients' behavioral/psychological symptoms than by their cognitive impairment. In the end, because of difficulties for daily care at home, the patients are sent to a dementia care home or another institution of that kind. Therefore, controlling the behavioral/psychological symptoms is important.<sup>2</sup> Common forms of the syndrome are Alzheimer's disease, vascular dementia, dementia with Lewy bodies (abnormal aggregates of protein that develop inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal lobe of the brain). Each of them may display different symptomatic patterns. The behavioral/psychological symptoms appear at

**Conflict of Interest**

The authors have no potential conflicts of interest.

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any phase of dementia, and some of them may be seen more frequently at a certain stage.<sup>1,3</sup> The symptoms that dementia patients have are similar to those of psychiatric disorders, but some are slightly different from each other. Therefore, clinical doctors should consider this fact when they practice therapies.

This review is aimed at helping understanding and treatment of neurobehavioral symptoms that are found in clinical trials during a clinical study of behavioral/psychological phenomenology, that are often seen in dementia patients, and that are overwhelming for the caregivers as well as themselves, along with their pathophysiology, evaluation, and treatment.

## STATUS OF BEHAVIORAL/PSYCHOLOGICAL SYMPTOMS IN DEMENTIA DIAGNOSIS

Behavioral/psychological symptoms are not considered under the current standards for dementia diagnosis, although most patients suffer from the symptoms as dementia progresses. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) and 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (revised in May 2013), some of the necessary criteria for dementia diagnosis are multiple cognitive functions and performance of daily activities. In the DSM-V (recently revised), the word dementia is replaced with a new term, neurocognitive disorder, redefining the range and definition. However, this revision does not add behavioral/psychological symptoms as the essential criteria. Nonetheless, the U.S. Food and Drug Administration (FDA) considers any improvement in cognitive functions and daily life performance as well as behavioral/psychological symptoms as an essential requirement for a new dementia remedy if a new medicine is developed, recognizing the importance of the factors.<sup>4</sup> That is, behavioral/psychological symptoms are critical indicators in reality to identify dementia, although the standards are excluded.

## INCIDENCE RATE

Incidence of behavioral/psychological symptoms differs according to the type of illness and progression phase. Studies until now have said that most dementia patients experienced at least one behavioral/psychological symptom during the onset.<sup>3</sup> The Cache County Study reported that 97% of dementia patients had shown at least one behavioral/psychological symptom for 5 years. Depression accounted for 77%, followed by apathy (71%) and anxiety (62%).<sup>1</sup> Studies on patients who had never taken medicine for dementia or behavioral/psychological symptoms found that the incidence rate of depression was the highest, and the other symptoms differ according to the onset of dementia.<sup>5</sup> Depending on the form of dementia, the incidence rate of each behavioral/psychological symptom may differ. Those who suffer from dementia with Lewy bodies are more likely to experience hallucinations than are those with Alzheimer.<sup>6</sup> Patients with Alzheimer are more likely to have delusions than are those with vascular dementia. On the other hand, patients with vascular dementia would experience depression, apathy, and mood disturbances<sup>7</sup> more. People with frontotemporal dementia, particularly, a behavioral variant type of frontotemporal dementia, are more likely to have impulsiveness, aggressiveness, disinhibition, compulsion, excessive sex drive, and personality disorders than are the others with different forms of dementia.<sup>8</sup>

## PHENOMENOLOGY

Behavioral/psychological symptoms differ among dementia patients, and there are also many unexpected conditions, which means that a single or mixed disorder of emotion, thinking, cognition, and motion is found in many cases. Aspects of depression seen in dementia patients may be different from those of general depression experienced by younger people. For this reason, it is hard to define or understand the behavioral/psychological symptoms. As a first step to understanding the symptoms that the patients have, one must carefully distinguish them from each similar symptom (e.g., depression vs. apathy). Of course, it is not easy to correctly identify which is which, since there are no diagnostic standards for such symptoms. Second, one must see if a symptom appears because of the environment that the patient faces in a clinical trial, or if it is caused by a disorder of the nervous system. If the symptom is about a secondary personality disorder, the risk factors should be controlled to resolve the issue. Last, one must decide whether the symptoms will be classified in detail according to each characteristic or if they will be labeled as groups according to each symptom. The steps may help us understand the illness in more detail and find common grounds between symptoms that look irrelevant to each other. They will be useful for a clinical trial or treatment for dementia.

### Emotional disorder

Depression is the most frequent symptom in dementia patients but is hard to define. The symptoms appearing in dementia have been known to be versatile and lacking in experience or research. For such reasons, it is hard to diagnose depression in patients with dementia. First, the patients not only are unaware of their condition but also cannot effectively express their emotions, because of a language or cognitive disorder accompanied by dementia. Second, it is hard to identify whether some physical symptoms usually found in depressive disorders (e.g., sleep disorder, appetite loss, or sexual dysfunction) are from dementia or just depression. Third, clinical aspects of depressive dementia and early-onset depression may be different.<sup>9</sup> Fourth, it is not easy to draw a line between depression and apathy. Last, for all the characteristics described above, the credibility and concordance rate of the depression test kit for dementia patients would fall.<sup>10</sup>

Let's consider an example. Looking at the DSM standards most widely used for depression diagnosis, the DSM-III focused more on *depressed mood*. However, the DSM-IV (relatively recent standards) emphasized *loss of interest or pleasure*, which is a common symptom not only of depressed patients but also of those without mood-disorder experience, leading to more diagnoses of mood disorder. To meet the most recent DSM-V standards, just as under DSM-III, people who go through the test need appropriate language ability and cognitive function to express their feelings of loss of interest or hopelessness. For dementia patients, such an ability may be damaged on a different level according to the onset. *Withdrawal or social isolation*, defined as a symptom of mood disorder, is often seen in Alzheimer's patients. Therefore, such symptoms are difficult to distinguish from each other.

There are differences between Alzheimer's disease and early-onset depression in incidence rate, family history, past medical history, severity level, suicide attempts, symptom duration, prognosis, and reactions to treatment. For example, Alzheimer's patients experience depressive symptoms as less severe than those with early-onset depression. They get better or worse repeatedly and rarely attempt suicide. Gender is not relevant, and socio-psychological factors are vague.<sup>9</sup> Often, depressed dementia patients do not express sad feelings. Rather, they feel unmotivated or loss of pleasure accompanied by delusions or apathy.<sup>11</sup>

Apathy can be defined as lack of motivation for goal-oriented activity, which is revealed by behavioral or emotional cognition.<sup>12</sup> But it can be misunderstood as a major depressive disorder, since patients with depression generally show lack of interest or energy, which is the main symptom of apathy.<sup>13</sup> Although lack of motivation is the common symptom seen in both apathy and depression, people with apathy do not feel depressed but just unmotivated. Identifying which is present is possible during a deep talk, but that may be hard, because such a talk requires a certain level of language ability, which patients often lack during the course of dementia.

Elevated mood ranges from hypomania to severe mania. Persons in such a mood feel extremely high, elated, euphoric, and full of energy, which is awkward in their situation. Anxiety and elation look extremely different, but they are similar, in that both are often connected to a hypersensitivity reaction or unhealthy emotions that patients get when they face any threat from external stimuli, as may be seen in dementia patients.<sup>5</sup> In addition, dementia patients often experience emotional instability. The mood may change just in minutes or even in seconds.

### **Delusions and thought disorder**

Delusions work differently in dementia patients depending on the cause, although mainly people with Alzheimer's or Lewy-body dementia experience them. Many of them are paranoid compared to that of schizophrenics, non-bizarre, and simple. Alzheimer's patients often experience a delusional misidentification, which is hardly seen from schizophrenics.<sup>14</sup> Complicated and bizarre delusions, particularly Schneider's first-rank symptoms, are not seen in people with dementia. It is also extremely rare to see delusional and depressed dementia patients attempt suicide. However, about 50% of schizophrenics attempt to kill themselves, and 10% die from suicide. In an earlier onset of dementia, patients are likely to be paranoid, but in the middle stage, they get involved in delusional misidentification; that is, delusions may differ according to pathophysiology.<sup>14,15</sup> Since the delusional misidentification, in particular, is seen in patients with Alzheimer's or Lewy-body dementia, it is worth diagnosing.<sup>16,17</sup> In the later onset of dementia, delusion seems to disappear, perhaps because the patients are unable to describe what they experience because of the deteriorated language ability.<sup>18,19</sup> Those suffering from dementia take a less-psychoactive drug for a shorter period of time than schizophrenics do in order to relieve symptoms or prevent recurrence.<sup>20,21</sup>

### **Cognitive disorder**

Dementia patients may experience cognitive disorders in all sensory areas. Many times, it is hard to distinguish a cognitive disorder from an illusion, sensory distortion, or a delusion that appears without a stimulus. Particularly, delusions are a common symptom appearing in dementia patients with Lewy bodies and Parkinson's disease. Those delusions appear repeatedly and usually have a concrete shape like a human or animal that patients describe well. They appear in typical patterns and complicated forms for each person. Delusions appear or disappear suddenly and seem very real but go away when the patients try to confirm them.<sup>22</sup> Meanwhile, Alzheimer's patients experience delusions in all sensory areas in the later onset, unlike those with Lewy-body dementia. They usually have visual or auditory hallucinations.<sup>23</sup> Especially, Alzheimer's patients are more likely to experience a delusion and hallucination at the same time, making them difficult to distinguish from each other.

### **Motor disorder**

Motor disorder does not mean motion dysfunction. It refers to multiple abnormal acts, such as wandering, repetitive but aimless acts, disinhibition, and socially unacceptable behaviors, such as lewd acts. It is relatively easy to define the motor disorder, as it is obvious to see

from observation (objective evaluation) as opposed to the other behavioral/psychological symptoms, which require an interview with patients (subjective evaluation). The dysfunction is divided broadly into 2: motion increase and motion decrease. Motor retardation refers to a slow motion or speaking and a decrease in voluntary movement. Motor hyperactivity represents being full of energy and excessive talk and movement. Wandering, aimless movement in a certain pattern, is one form of the motor hyperactivity, which when combined with a sleep disorder can hugely affect the quality of life of both the patient and the family.<sup>24</sup>

Agitation is a feeling of aggravation, annoyance, or restlessness brought on by provocation—or, in some cases, little to no provocation. The symptom is a big burden for the patient, family, and caregivers.<sup>25</sup> Cohen-Mansfield classified agitation into 4 categories:

- (1) Physically non-aggressive behavior;
- (2) Verbally non-aggressive behavior;
- (3) Physically aggressive behavior;
- (4) Verbally aggressive behavior.

Both care recipients and care givers may take this very hard, but it can be greatly improved by having a better environment before taking medicine, because agitation is largely linked to the external environment.

### **Change in circadian rhythm**

Humans each have different circadian rhythm by day and night, season, and year. Light works on hypothalamic suprachiasmatic nuclei and controls the circadian rhythm. Alzheimer's patients may suffer from severe sleep disorders at the early stage because of pathological (toxic) aggregates of amyloid protein in the hypothalamic suprachiasmatic nuclei.<sup>26</sup>

Dementia patients mostly complain about hypersomnia, insomnia, irregular sleep and wake cycles, fragmented sleep, and rapid eye movement sleep behavior disorder. Such a change in sleep patterns leads to a poor quality of sleep, getting the patients' days and nights mixed up. Caregivers may be exhausted.<sup>27</sup> However, there are various factors that cause changes in circadian rhythm, such as pain, urination at night, diuretics, brain stimulants, and other drug use. Therefore, many different factors should be considered.

### **Eating disorder**

In theory, appetite is controlled by homeostatic and hedonic pathways, and neurotransmitters or brain lesions linked to that are seen in dementia patients. A change in appetite is not common for dementia patients at the early stage. Over time, they may resist a meal or have no interest in food. Conversely, they may be obsessed with a certain or improper food or feel difficulty in swallowing, which could become a big challenge for the caregiving family.<sup>28</sup> The change may be either quantitative (appetite loss or overeating) or qualitative (obsession with a certain food). For example, patients with frontotemporal dementia may be obsessed with sweets or high-carbohydrate foods.<sup>28</sup>

## **ASSESSMENT OF BEHAVIORAL/PSYCHOLOGICAL SYMPTOMS**

To assess behavioral/psychological symptoms, it is necessary to record in detail the past medical history, subjective symptoms that patients experience, and objective acts, learned

not only from patients but also from family members and other caregivers. Although a patient with cognition dysfunction is not easy to communicate with, a one-on-one interview with open-ended questions (which enable one to see various reactions) are recommended before asking more organizational or standardized questions. Through an interview with caregivers, one can gain an objective understanding about the patient's symptoms and the caregivers' interest. The main interest of a caregiver or doctors may be different from that of the patient, and that difference may affect the patient's treatment.<sup>10</sup> If available, an interview with other caregivers in a different environment would be helpful for understanding the patient's condition in a diversified way. Any difference in opinion found between different caregivers may result from individual characteristics, but still the information exchange is important.

There are 2 types of organized quantification assessment tools for understanding dementia patients' behavioral/psychological symptoms. One is to see the overall symptoms; the other is to see a specific symptom. The first-category tool is Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD)<sup>29</sup> or Neuropsychiatric Inventory (NPI).<sup>30</sup> They categorize and score various kinds of behavioral/psychological symptoms seen in dementia patients. The tools, which have passed a validity test, are being used for clinical trials and research. Such assessment tools should be selected based on a clear purpose, for example, whether you see the behavioral/psychological symptoms on the whole or specifically, and whether you use the data in a clinical trial or for the purpose of study.

## CORRELATION BETWEEN AND PROGRESS OF SYMPTOMS

Behavioral/psychological symptoms in people with dementia differ. It is largely controversial if all kinds of symptoms can be classified into a single category, and each symptom is separate or heterogeneous, as is often described in assessment tools (12 symptoms in NPI) or if the syndrome can be divided into 3 or 4 categories. It is still hard to know how many groups are needed to divide the symptoms, because each symptom is different in each clinical trial. Nonetheless, certain symptoms tend to appear at the same time or get connected with each other. If you can clearly divide behavioral/psychological symptoms as homogeneous symptoms, the versatile and heterogeneous symptoms can be better understood, which will be helpful for treatment and prognosis.<sup>31</sup> There has been much research using various methods. There is a difference in each method, but usually psychosis (including delusions and hallucination) and mood (including depression and anxiety) are classified as the same category. The number of categories is usually 3 to 4.<sup>32,33</sup> Somewhat different research distinguishes delusions from hallucinations.<sup>5</sup> Different results can be explained by a difference in research methods, medicine use, and the research group. It could be said that there are 3 to 4 individual behavioral/psychological symptoms, but their clear classification has not been successful, since each method is different. Still, the current status of studies will help us understand the correlations between and among symptoms and treat patients better.

## PATHOPHYSIOLOGY

It has not been well known why dementia patients experience behavioral/psychological symptoms. However, it is known that genetic, neurobiological, personal (e.g., sex, age, or personality), and social (e.g., social environment, personality of the family caregiver) factors are related to the symptoms in various ways.

### Neurobiological factors

Behavioral/psychological symptoms, in many cases, appear for a genetic reason. Particularly, a genetic cause of Alzheimer's disease has been much studied. A correlation between the E4 subtype out of the ApoE genotype and behavioral/psychological symptoms has been reported, but it is still not clear.<sup>34,35</sup> A correlation between Alzheimer's patients with psychosis and a polymorphism in the neuregulin-1 and catechol-O-methyltransferase genes,<sup>36,37</sup> interleukin 1- $\beta$  gene, polymorphisms of dopamine receptor genes and the serotonin system gene, HTR2A has also been reported.<sup>38-40</sup> However, the results were not consistent in another study demonstrating no relevance.<sup>41</sup>

Dementia patients experience various changes in neurotransmitters, and this is related to behavioral/psychological symptoms. A change in the cholinergic nerve system from both Alzheimer's patients and those with Lewy-body dementia has been reported, but the change aspects are different, leading to a difference in behavioral/psychological symptoms.<sup>42</sup> Another study reported that changes in dopamine and the noradrenalin nerve system lead to aggressiveness.<sup>18,43</sup> Moreover, a decrease in serotonin and change in glutamate concentration are related to psychosis or aggressiveness.<sup>44,45</sup>

In pathological structure, brain weight loss, neurofibrillary tangle lesions in the parahippocampal gyrus, frontal lobe, or parietal lobe, and nerve damage on the hippocampus and Meynert basal ganglia may lead to behavioral/psychological symptoms.<sup>46</sup> In particular, psychosis appearing in Alzheimer's patients is relevant to neurofibrillary tangle lesions in the neocortex.<sup>47</sup> According to another report, the behavioral/psychological symptoms appearing in Alzheimer's disease are related to cerebrovascular illness rather than degenerative pathology.<sup>48</sup> Thus, any genetic, pathological, or physiological issue cannot be a single cause, although they all have relevance. Those factors with a mix of social and individual environments lead to the symptoms.

### Neuroimaging and behavioral/psychological symptoms

There are various kinds of research on imaging in relation to the behavioral/psychological symptoms of dementia patients. Neuroimaging found anterior cingulate and hypo-metabolism in the frontal lobe in depressed Alzheimer's patients.<sup>49</sup> Moreover, it enables one to distinguish apathy from depression for Alzheimer's patients. In Alzheimer's patients with apathy, metabolism in the left orbitofrontal lobe is meaningfully lowered, whereas in those with depression, hypo-metabolism occurs in the dorsolateral prefrontal lobe.<sup>50</sup> Alzheimer's disease with psychosis leads to a reduced blood flow in the right orbitofrontal lobe and dorsolateral prefrontal lobe cortex, asymmetry<sup>51</sup> in the prefrontal lobe and temporal lobe, and hypo-metabolism in the prefrontal lobe.<sup>52</sup>

In a quantitative brain MRI of frontotemporal dementia patient with apathy, a brain shrinkage was seen in the right caudate nucleus, temporoparietal lobe, temporal gyrus, and left frontal operculum.<sup>53</sup>

### Other factors

Regardless of the cause of dementia, various factors may be related to its behavioral/psychological symptoms. Duration or onset of the disease also may have relevance, and each symptom may appear more often in a certain stage.<sup>54</sup> Age and sex also may be connected to a certain symptom. The Cache County Study found that women were more likely to have delusions and anxiety than men are, and the older the patients were, the less anxiety they experienced. Delusions were experienced by women more than by men, whereas abnormal

motion acts were more common for men than for women. According to other studies, age or sex does not affect behavioral/psychological symptoms. Rather, alcohol consumption, trauma, or a stroke history before the disease may play a role.<sup>55</sup> Personal characteristics like neuroticism or psychological factors before the disease develops lead to anxiety or delusion.<sup>20</sup> Environment that is not related to the patient also may affect the symptoms. For example, patients living in an institutional facility who have less private care or emotional exchange are more likely to experience behavioral/psychological symptoms.<sup>55</sup>

## CONCLUSION

Behavioral/psychological symptoms are not unusual, regardless of the form of dementia causing hardships for patients, caregivers, and society across the board. The symptoms, however, have no single cause or homogeneous feature. Often, multiple (homogeneous or heterogeneous or mixed) symptoms appear at the same time. Therefore, it is necessary to use a multifaceted way to assess them, sometimes using the systematic assessment tool. Once you understand the symptoms, a non-pharmacological or pharmacological approach should be taken to control the symptoms.

Although we have various ways to control them, only a symptomatic approach is available, because the root cause of the neurobehavioral symptoms of dementia is not yet known. The treatment can be limited because of the form of dementia, body condition, and multiple social factors. In this context, for the treatment of the neurobehavioral symptoms of dementia, it is critical to work continuously and organically with patients, caregivers, and doctors. The social environment is also important. Thus, the neurologists who mainly care for dementia and want to help patients and their caregivers should keep up with or expand their knowledge about neurobehavioral symptoms, updating the recent news and new therapy.

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