Capgras Syndrome and Its Relationship to Neurodegenerative Disease

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Background: Capgras syndrome is characterized by a delusional belief that a person has been replaced by an imposter. It has been described in psychiatric and neurological (neurodegenerative and nonneurodegenerative) diseases.

Objectives: To determine whether the clinical and demographic features of subjects with Capgras syndrome differ when the syndrome is associated with neurodegenerative compared with nonneurodegenerative diseases, and whether features differ across different neurodegenerative diseases.

Design: Retrospective study.

Setting: Tertiary care medical center.

Patients: Forty-seven subjects with Capgras syndrome.

Results: Thirty-eight of the subjects with Capgras syndrome (81%) had a neurodegenerative disease, most commonly Lewy body disease. Capgras syndrome occurred at a younger age of onset in those with a nonneurodegenerative disease (51 vs 72 years) ($P < .001$) co-occurring with paranoid schizophrenia, schizoaffective disorder, and methamphetamine abuse and immediately after cerebrovascular events. Of those with Capgras syndrome and Lewy body disease, 100% had visual hallucinations compared with only one of those with Alzheimer disease (14%).

Conclusions: Capgras syndrome is more commonly associated with neurodegenerative diseases, especially Lewy body disease, where visual hallucinations always coexist. In the absence of a neurodegenerative disease, the onset of Capgras syndrome occurs at a significantly younger age and can be associated with psychiatric disease, cerebrovascular events, and illicit drug use.

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The Capgras syndrome was described almost a century ago. It is characterized by the recurrent and transient (ranging from minutes to months) belief that a person, usually someone closely related, has been replaced by an imposter. The imposter usually has features that are very similar to those of the original person, although subtle physical differences are used to differentiate the original person from the imposter.

Capgras syndrome is assumed to be a rare phenomenon initially reported to be associated only with psychiatric diseases, including paranoid schizophrenia and schizoaffective disorder. However, more recently Capgras syndrome has also been described in neurological conditions including epilepsy, in cerebrovascular disease, after head trauma, with pituitary tumor, and especially in neurodegenerative diseases such as Alzheimer disease and Lewy body disease. However, it is unknown whether there are differences between Capgras syndrome that occurs in neurodegenerative compared with nonneurodegenerative diseases, or whether there are differences in Capgras syndrome when it occurs in different neurodegenerative diseases.

The aims of this study were to determine (1) whether the occurrence of the Capgras syndrome is limited only to the disorders in which it has been previously described, (2) whether clinical and demographic features of subjects with Capgras syndrome associated with neurodegenerative diseases differ from those of subjects with Capgras syndrome associated with nonneurodegenerative diseases, and (3) whether clinical features and demographics of subjects with Capgras syndrome differ when the syndrome is associated with different neurodegenerative diseases.

METHODS

SUBJECTS

The Mayo Clinic Medical Records Linkage System was used to identify all subjects who underwent evaluation at this institution and had Capgras syndrome from January 1, 1996,
through December 31, 2006. This system was queried to capture all medical records in which the term Capgras or misidentification had been used by the evaluating physician. Therefore, any subject in whom Capgras syndrome or misidentification syndrome had been mentioned as absent or present by the evaluating physician would have been captured.

The medical records of all subjects identified were then reviewed to determine whether the description of Capgras or misidentification syndrome met inclusion criteria for Capgras syndrome. Specifically, to be included in this study, the description of Capgras phenomenon clearly had to be a delusional belief that someone had been replaced by an imposter. In addition, the description of the phenomenon had to be transient, repetitive, and documented in multiple medical records from different times. A subject was excluded if the description of Capgras syndrome recorded in the medical records was not clearly a delusional belief that a person was replaced by another. Specifically, subjects were excluded if the description was more suggestive of a lack of facial recognition (prosopagnosia).

Clinical diagnosis at the time Capgras syndrome was diagnosed was recorded. Visual hallucinations, auditory hallucinations, parkinsonism, rapid eye movement sleep behavior disorder, fluctuations, and memory loss were recorded as absent or present at the time of the evaluation documenting the presence of Capgras syndrome. These features were chosen because Capgras syndrome has been described in Lewy body disease and Alzheimer disease.\textsuperscript{7,13-17} Parkinsonism was defined as the presence of 2 or more of the following: cogwheel rigidity, stooped posture, shuffling gait, bradykinetic alternating motor rates, facial masking, and resting tremor. Only spontaneous, well-documented parkinsonism was included. Postural tremor or drug-induced parkinsonism was excluded. Rapid eye movement sleep behavior disorder was considered present if the behavior met diagnostic criteria B for rapid eye movement sleep behavior disorder, defined as abnormal, wild flailing movements occurring during sleep (with sleep-related injuries) or sleep behavior disorder, defined as abnormal, wild flailing movements occurring during sleep (with sleep-related injuries) or movements that are potentially injurious or disruptive.\textsuperscript{18,19} The medical records were also reviewed for the bedside Short Test of Mental Status score\textsuperscript{19} and to determine whether the subject met Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) (DSM-IV-TR) criteria for dementia\textsuperscript{20} at the time of documentation of Capgras syndrome.

To accomplish aims 2 and 3, all subjects who met criteria for Capgras syndrome were separated into group 1, which consisted of subjects with Capgras syndrome and a neurodegenerative disease, and group 2, which consisted of subjects with Capgras syndrome and a nonneurodegenerative disease.

SUBDIVISION OF GROUP 1 SUBJECTS

Subjects in group 1 were subdivided into subgroups 1A, 1B, and 1C. These subgroups were chosen because Capgras syndrome has been described in Lewy body disease and Alzheimer disease.\textsuperscript{13-17} Subgroup 1A consisted of subjects from group 1 who had been given a diagnosis of Lewy body disease by a behavioral neurologist at the time Capgras syndrome was documented. Subgroup 1B consisted of subjects from group 1 who had been given a diagnosis of Alzheimer disease by a behavioral neurologist at the time Capgras syndrome was documented. Subgroup 1C consisted of the remainder of subjects from group 1 who had been given a diagnosis of a neurodegenerative disease other than Lewy body disease or Alzheimer disease by a behavioral neurologist at the time Capgras syndrome was documented. (In this study, the term Lewy body disease encompasses idiopathic Parkinson disease, dementia with Lewy bodies, and Parkinson disease dementia.)

STATISTICAL ANALYSES

Statistical analyses were performed using JMP statistical software (JMP, version 6.0.0; SAS Institute Inc, Cary, North Carolina), with statistical significance set at $P < .05$. Sex ratios and binary variables collected (presence or absence of hallucinations, parkinsonism, fluctuations, rapid eye movement sleep behavior disorder, and dementia) were compared across groups and subgroups using the $\chi^2$ test and Fisher exact test for cells with small numbers. Demographic features, including age at disease onset and age at Capgras syndrome onset, and the Short Test of Mental Status scores\textsuperscript{19} were compared across groups and subgroups using the analysis of variance test.

RESULTS

A total of 165 subjects were identified by the Medical Records Linkage System. Of these, 109 subjects had been identified because the evaluating physician had specifically assessed for Capgras syndrome or a misidentification syndrome and had documented that the syndrome was absent (ie, “absent Capgras syndrome” or “absent misidentification syndrome”). In addition, 9 subjects were excluded because the description of Capgras syndrome did not meet the inclusion criteria.

DIAGNOSES

Forty-seven subjects had documentation of Capgras syndrome. Thirty-eight of these 47 subjects had been diagnosed as having a neurodegenerative disease, including Lewy body disease (26 patients), Alzheimer disease (7), dementia not otherwise specified (3), frontotemporal dementia (1), and aphasic dementia (1). In the subjects with a neurodegenerative diagnosis, Capgras syndrome was documented at presentation in 2 subjects, both whom had received a diagnosis of dementia with Lewy bodies.\textsuperscript{21} Of the remaining 9 subjects who did not have a neurodegenerative disease, 2 had a primary psychiatric diagnosis of paranoid schizophrenia and schizoaffective disorder. One of these subjects had the onset of Capgras syndrome at 20 and the other at 17 years of age. The 2 subjects with Capgras syndrome in the context of methamphetamine abuse had onset at 37 and 38 years of age. Of the remaining 5 subjects, 2 had the acute onset of Capgras syndrome immediately after an intracerebral hemorrhage. Another subject had onset after undergoing right temporal lobectomy for necrotizing meningoencephalitis, another while recovering from septic shock in the intensive care unit, and the last after an acute right temporoparietal ischemic infarct. In the 2 subjects with intracerebral hemmorages, the location of the hemorrhage was in the right frontal lobe after surgical resection of a brain tumor in the first subject and in the left temporal lobe with superimposed diffuse subarachnoid hemorrhage after administration of thromboplastin and heparin sulfate for an impending myocardial infarction in the second subject.

IMAGING

All subjects underwent magnetic resonance imaging or computed tomography of the head at least once. In most of the
The description of Capgras syndrome was similar for all subjects. It is (reduplicative paramnesia)23 and the delusion that one is (reduplicative paramnesia)23 and the delusion that one's house is not where it is (reduplicative paramnesia).23 and the delusion that there are other people present although not seen (extra-campine hallucinations).24 In the latter delusion subjects believed that other people were living in their home because they could “feel their presence.” Rarer delusions included those of being raped or of killing someone and misidentification of oneself when looking in the mirror. Some subjects also exhibited paranoid behaviors; for example, 1 subject would not use the telephone because he believed others were conspiring against him.

GROUP COMPARISONS

The 47 subjects with Capgras syndrome were divided into those with a neurodegenerative disease (group 1; n=38) and those without a neurodegenerative disease (group 2; n=9). The characteristics of Capgras syndrome were similar in subjects with and without a neurodegenerative disease. All 38 subjects with a neurodegenerative disease had memory loss and also met DSM-IV-TR criteria for a diagnosis of dementia,20 with a mean score of 20 on the Short Test of Mental Status (highest possible score, 38; range, 5-29).19 Only 2 subjects without a neurodegenerative disease had memory loss, which in 1 met DSM-IV-TR criteria for dementia.20 Those without a neurodegenerative disease had the onset of Capgras syndrome at a significantly younger age (mean, 51 years) compared with those with a neurodegenerative disease (mean, 72 years) (P<.001). Visual hallucinations occurred more frequently in those with a neurodegenerative disease (30 subjects) compared with those without (2) (P=.003) at the time Capgras syndrome was first documented.

PATHOLOGICAL FINDINGS

Only 2 subjects underwent a postmortem evaluation: one with a clinical diagnosis of Lewy body disease (subgroup 1A) and the other with a clinical diagnosis of Alzheimer disease (subgroup 1B). Pathological findings in both subjects included neocortical Lewy bodies,21 and the group 1A subject also had pathological changes consistent with Alzheimer disease.22 The group 1B subject was recorded to have had visual hallucinations at the time Capgras syndrome was documented.

CAPGRAS SYNDROME DESCRIPTION AND OTHER DELUSIONS

The description of Capgras syndrome was similar for all subjects, independent of sex. Examples are described in the Table. In 40 of the 47 subjects, the delusion involved the subject’s spouse; most delusions involved an imposter of the same sex replacing the spouse. In some instances, there was more than 1 replacement. In 1 subject, for example, there were 6 imposters, all with the same name. Another subject went to his priest and confessed that he had committed a sin because he had married more than 1 woman. In 5 of the other 7 subjects, Capgras syndrome involved the subjects’ children; in the other 2 subjects, other relatives. Twenty-eight of the 47 subjects had additional delusions. Some were more common than others; for example, the delusion that one’s house is not where it is (reduplicative paramnesia)23 and the delusion that there are other people present although not seen (extra-campine hallucinations).24 In the latter delusion subjects believed that other people were living in their home because they could “feel their presence.” Rarer delusions included those of being raped or of killing someone and misidentification of oneself when looking in the mirror. Some subjects also exhibited paranoid behaviors; for example, 1 subject would not use the telephone because he believed others were conspiring against him.

SUBGROUP COMPARISONS

The 38 subjects in group 1 with a neurodegenerative disease were further subdivided into those who had been given clinical diagnoses of Lewy body disease (subgroup 1A; n=26), Alzheimer disease (subgroup 1B; n=7), and other neurodegenerative diseases (subgroup 1C; n=5). All 26 subjects with a diagnosis of Lewy body disease met published research criteria for dementia with Lewy bodies (n=16) or Parkinson disease dementia (n=10).21 There was a significant difference between subgroups for frequency of visual hallucinations, parkinsonism (P<.001 for both), and rapid eye movement sleep behavior disorder (P=.006). Of the subjects with Lewy body disease (subgroup 1A), those who met criteria for dementia with Lewy bodies21 had the onset of Capgras syndrome a mean of 3 years after disease onset, a significantly shorter time than those who met criteria for Parkinson disease dementia (onset of Capgras syndrome, a mean of 8 years after disease onset) (P=.04). In those with Parkinson disease dementia, the onset of Capgras syndrome occurred a mean of 2 years after the onset of dementia.

COMMENT

This study extends the spectrum of diseases in which Capgras syndrome has been previously described, demonstrates differences in the demographics of subjects with Capgras syndrome when it occurs in the context of a neurodegenerative vs a nonneurodegenerative disease, and shows differences in the demographics of subjects with Capgras syndrome between different neurodegenerative diseases.

There were no differences between men and women in terms of the descriptions of Capgras syndrome. Both were equally likely to experience the syndrome in relation to a spouse. This is not surprising because Capgras syndrome is known to involve intimately associated persons. In many of our subjects, Capgras syndrome involved multiple imposters and additional delusions, including misidentification of familiar places (reduplicative paramnesia)23 and the belief that there were other per-
sions present in the house (extracampine hallucinations). The association of Capgras syndrome and reduplicative paramnesia has been reported, and it has been suggested that both diseases have common underlying anatomic dysfunction or cognitive deficiencies. Reduplicative paramnesia is believed to involve the frontal lobe, and 1 subject in this study had right frontal lobe lesions with immediate development of Capgras syndrome. Arguing against this frontal lobe hypothesis that others have proposed is the fact that most of the subjects in this study had magnetic resonance imaging or computed tomography of the head that showed variable amounts of global atrophy, and 3 subjects with acute onset of Capgras syndrome had the lesions located in the temporal and parietal lobes. Therefore, frontal lobe damage may not be the cause of Capgras syndrome but a disconnection of the other lobes from the frontal lobe. This occurred mainly with right hemisphere lesions in our subjects with acute onset of the syndrome.

In this study, Capgras syndrome occurred more commonly with neurological diseases, especially neurodegenerative disease. Thirty-eight subjects (81%) had Capgras syndrome in the context of neurodegeneration. These subjects were significantly more likely to have the onset of Capgras syndrome at an older age compared with those without a concurrent neurodegenerative disease. In those who presented with features of idiopathic Parkinson disease, the onset of Capgras syndrome occurred at a mean of 8 years later, when all of the subjects had become demented and met criteria for Parkinson disease dementia.

Visual hallucinations were more commonly associated with Capgras syndrome in the context of a neurodegenerative disease. This was being driven by the high prevalence of subjects who met criteria for Lewy body disease in group 1, because 26 of the 38 group 1 subjects (68%) were classified as having Lewy body disease, and all had visual hallucinations. Visual hallucinations are a common feature in Lewy body disease. However, only 46% of subjects with Lewy body disease would be expected to have visual hallucination. Therefore, the 100% co-occurrence of visual hallucinations and Capgras syndrome in the subjects with Lewy body disease suggests that, in Lewy body disease, Capgras syndrome and visual hallucinations may have a common etiopathogenesis.

Although the majority of subjects in group 1 were diagnosed as having Lewy body disease, more than one-third initially presented with motor impairment, especially resting tremor, and were initially diagnosed as having idiopathic Parkinson disease. These subjects later became demented and were diagnosed as having Parkinson disease dementia. Because Capgras syndrome was not noted to occur during the period when clinical symptoms were consistent with a diagnosis of Parkinson disease but occurred later when dementia was present, one can argue that Capgras syndrome is associated with neocortical dysfunction.

From this study, one may argue that the co-occurrence of visual hallucinations and Capgras syndrome strongly suggest a diagnosis of Lewy body disease. Actually, the subject with Capgras syndrome, Alzheimer disease, and autopsy confirmation, also had pathologically confirmed Lewy bodies. This subject had visual hallucinations. Capgras syndrome was also documented in 5 subjects with other neurodegenerative demen- tias. In 2 of these, the clinical diagnoses of aphasic dementia and frontotemporal dementia were rendered at the time of evaluation, and in the other 3, dementia was not otherwise specified. These findings imply that Capgras syndrome may be seen in neurodegenerative diseases other than Lewy body disease and Alzheimer disease. It is very important to have autopsy confirmation in these subjects because different neurodegenerative diseases can have overlapping clinical features.

In this study we identified 9 subjects with Capgras syndrome who were not believed to have an underlying neurodegenerative disease. Less than 25% of these (2 subjects) had a primary psychiatric disease. It is possible that the smaller number of subjects with a psychiatric disease results from an ascertainment bias because the prevalence of Capgras syndrome has been reported to be as high as 15% in some series, although one series reported only 4% prevalence. We also identified 2 subjects who developed Capgras syndrome immediately after methamphetamine abuse. To the best of our knowledge, this is a novel finding that suggests that Capgras syndrome may be related to dopamine dysregulation because methamphetamine causes the loss of dopamine transporters. This would also explain the high association of Capgras syndrome with Lewy body disease, in which there is also loss of dopamine transporters due to neuronal loss. Others have also suggested dopamine dysfunction in Capgras syndrome. An additional 3 subjects presented with Capgras syndrome after acute cerebrovascular insults, suggesting that Capgras syndrome may occur from destruction of focal neocortex. In all subjects, however, the lesions were quite extensive, involving a significant amount of neocortex. One of these had a large right frontal lobe hemorrhage, another had a large left temporal lobe hemorrhage with superimposed diffuse subarachnoid bleeding, and the third had a right middle cerebral artery territory infarct affecting the temporal and parietal lobes. Others have also reported Capgras syndrome after cerebrovascular events including subarachnoid bleeding. In addition to these hypotheses of focal neocortical damage and dopamine dysfunction causing Capgras syndrome, there are other hypotheses concerning the etiology of the phenomenon.

This study demonstrates that Capgras syndrome occurs relatively more frequently with neurodegenerative diseases, especially Lewy body disease, but can also occur after cerebrovascular events, with illicit drug use, and with psychiatric diseases. When Capgras syndrome is associated with neurodegeneration, there is likely an older age at onset than if it were associated with a nonneurodegenerative disease. Capgras syndrome occurring in the context of a dementia where visual hallucinations are also present suggests Lewy body disease.

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REFERENCES


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