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Journal of Neurology & Translational Neuroscience

Research Article

The Neuropsychological Characteristics of Misidentification Syndrome

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Submitted: 30 July 2013

Accepted: 16 August 2013

Published: 19 August 2013

Keywords
- Misidentification syndrome
- Delusions
- Paranoid
- Neuropsychological characteristics
- Missing values

Abstract

Background: Although misidentification syndrome (MIS) is a relatively common psychiatric symptoms in Alzheimer's disease (AD), there has not been a lot of research for clinical and neuropsychological characteristics of this syndrome. To find the disproportionate neuropsychological deficit of patients with MIS compared to patients with paranoid and non-delusion, this study delineates the aspect of missing values and compares each neuropsychological test between MIS and other groups.

Methods: Psychotropic-naïve(drug-naïve) K-MMSE matched probable AD patients with MIS(26), paranoid delusion(25), and non-delusion(31) were assessed with the Seoul Neuropsychological Screening Battery, which included measures of memory, intelligence, and executive functioning.

Results: Patients with MIS had lower scores in the Rey-Osterrieth Complex Figure Test copy, Controlled Oral Word Association Test, and Color Word Stroop Test compared to patients with paranoid delusions. The Seoul Verbal Learning Test immediate recall was lower in MIS compared to other groups. Only the missing values in contrast program and go/no-go test were significantly higher in MIS compared to other groups. After the replacement of the missing values of go/no-go test and contrast program, these tests showed significantly lower scores in MIS group compared to other groups and paranoid groups.

Conclusions: Our study showed that MIS is disproportionately cognitive deficit suggesting left temporal, right parietal and both frontal dysfunction (especially in right frontal). Considering neuropsychological differences between MIS and paranoid delusions, these symptoms may have different pathophysiological anatomic substrates.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease characterized by impairment in memory, visuospatial function, language, executive function. In addition to these cognitive impairments, most patients suffer from psychotic symptoms such as delusions and hallucinations.

However, recent epidemiological [1], genetical [2], neuropathological [3], and neuropsychological [4,5] research has suggested that Alzheimer's disease with delusions can be discussed separately from hallucinations. Furthermore, even delusion can be subtyped, which may have different anatomical substrates.

Although the association between delusions and general cognitive dysfunctions in AD has been reported [5-8], the association between delusions subtypes and specific cognitive deficit has been rarely examined. In demented patients, the manifestation of delusions is thought to result from the executive dysfunction [7,8]. Jeste reported a significant association between delusions in AD and poor performance on category fluency [5], whereas there was no significant association between delusions and deficits on other neuropsychological tests. Although various disputable results have been demonstrated in previous studies, some neuroimaging studies support a relationship between neuropsychological frontal lobe dysfunction and delusions in patients with AD.

Phenomenologically, delusions can be classified into two distinct subtypes, i.e. misidentification syndrome (MIS) and paranoid delusion [9]. These subtypes showed different epidemiological and clinical characteristics. Therefore to understand the neuropsychological characteristics of delusions, delineating the delusions subtypes are essential.

Perez- Madrinan reported that AD patients with misidentifications had more severe deficits on copy and immediate recall of the Rey-Osterrieth Complex Figure and the verbal fluency than AD patients without psychotic symptoms [9]. However, there are still considerable debates on whether specific neuropsychological differences exist among paranoid delusion, MIS and non-delusional, if general cognitive function is adjusted among study groups.

Most previous studies for delusion subtypes have been limited for several reasons. First, they included a significant proportion of medicated patients. As a result, these patients were exposed to various psychoactive medications including antipsychotics, antidepressants, cholinesterase inhibitors, etc. These medications may possibly have selectively or non-selectively influenced the delusion itself and neuropsychological test performance, thereby confusing the results.

Another problem is that MIS is mostly occurs in moderate to severe stages of dementia, whereas paranoid delusions usually occur in more mild stages of dementia compared to MIS [9]. So comparison of these two groups usually showed the difference of global cognitive status, and this may make it difficult to find the characteristic cognitive dysfunctions of MIS. For example, the Perez-Madrinan study seemed to find distinct clinical characteristics of MIS but after adjusting for global cognitive status (MMSE scores), none of these differences remained significant. This means that the neuropsychological characteristics of MIS in this study are not trait, but disease stage dependent factors, and there are no specific neuropsychological defects in MIS.

Finally, because MIS usually occurred in moderate to advanced stage of dementia, certain neuropsychological tests can be left unfinished. As a result, there is a possibility that missing values may have influenced overall results of other previous studies. However, most of studies did not consider the influence of missing values, and did not analyze these effects. Perhaps the analysis of missing value patterns can provides a clue for additional neuropsychological characteristics of delusion subtypes.

Generally, if missing values present in substantial portions of research population, increasing the sample population may be a proper statistical solution. However, if this is not feasible, missing values may skew the calculated statistics. Furthermore, if the mechanism of missing value occurs not at random, simply increasing the study populations may be futile and the results can be misleading.

The study exploring missing values (or non-response) on the MMSE showed that non-response does not randomly occur and scoring non-response as an error is actually related to severity of dementia [10]. Due to these missing values, the neuropsychological tests were biased toward the null effect. Therefore, our study considered that missing values in MIS may have the possibility of obscuring the characteristic cognitive dysfunction of the AD patients with MIS. However, the failure to perform a certain neuropsychological test does not always imply a specific cognitive deficit, but can be more likely to reflect other non-cognitive factors. Missing values due to non-cognitive reasons were excluded from this study.

The aims of this study were the followings. Firstly, we delineated the delusion subtypes. Secondly we examined the pattern of missing values and if there were any missing values considered as not having randomly occurred, replaced that value using missing value analysis. And finally, we explore the differences of neuropsychological tests among non-delusion, paranoid delusion and MIS.

METHODS

Participants

We conducted a retrospective review of 1237 patients with dementia from March 2003 to December 2012 at the Hyoja Geriatric Hospital, using the Hyoja Registry which describes all clinical, laboratory, and radiological information. If dementia was suspected, additional comprehensive neuropsychiatric assessments were routinely conducted. From this initial screening, computerized K-MMSE matched 82 patients with probable AD (these patients were never medicated before visiting our center) were recruited to be the subjects of this research. Among them, 25 patients were suffering from paranoid delusions (not combined with MIS), 26 patients had MIS(not combined with paranoid delusions) and the remaining subjects had no delusions(non-delusion). All subjects included in this study met National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD [11]. The patients were psychotropic-naïve(drug-naïve), except for episodic hypnotics that were taken for sleep difficulties. Patients taking psychotropic drugs, including antipsychotics, anticonvulsants, antidepressants, cholinesterase inhibitors, and benzodiazepines and not educated were excluded from this analysis.

The diagnostic evaluation included a medical history, a physical and neurological examination, a comprehensive neuropsychological test, a routine laboratory test, and brain magnetic resonance imaging (MRI) or computed tomography (CT) scans. The age at onset of the dementia was defined the time of onset of memory disturbances that exceeded the episodic forgetfulness. After a complete description of the study was given to the subjects, and the caregivers, written informed consent was obtained from the patients or caregivers.

Procedures

We assessed the presence of delusions by a semi-structured caregiver interview using the delusion scale of the Korean Neuropsychiatric Inventory (K-NPI) [12], which is informant-based rating scale for the behavioral and psychological symptoms in dementia patients. If he or she held the same delusion for the previous four weeks, this patient was considered to have delusions. Delusions secondary to delirium, drug toxicity, or other acute factors were excluded from this study.

We also assessed the different types of delusions using sub-questions from the K-NPI subscale. Using these sub-questions, paranoid and misidentification delusions were defined in accordance with the agreement of one neurologist and one psychiatrist independent of this study. Paranoid delusions included delusions of theft, persecutory, infidelity, and abandonment. Misidentification delusions included delusions of Capgras, phantom boarder, reduplication place, TV sign and mirror sign. The patients with combined paranoid and misidentification delusions were excluded from this study. Only pure paranoid delusion and pure misidentification were subjects of this study. To exclude other dementia except AD, patients who presented with prominent Parkinsonism, pronounced visual hallucinations, fluctuating level of consciousness, a history of falls and step-wise declining were excluded. Patients who had never experienced delusions were considered non-delusional.

Because misidentification delusions tend to occur in more severe dementia and less frequently compared to other groups, among the data set of our registry, the patients with paranoid delusions and non-delusion who matched K-MMSE with MIS were recruited as study subjects. In order to assess global dementia severity, the Korean version of the MMSE(K-MMSE) [13], Clinical Dementia Rating Scale(CDR) [14], and Clinical Dementia Rating Scale-Sum of Boxes(CDR-SB) was used. A Barthel index [15] for the activities of daily living (ADL) evaluation, and Geriatric Depression Scale (GDS) [16] for depression were also used to assess the subjects. After a complete description of the study was given to the subjects and the caregivers, written informed consent was obtained from either the patient or caregivers.

Neuropsychological examinations

All study subjects underwent the Seoul Neuropsychological Screening Battery (SNSB) [17], a neuropsychological tests battery that includes validated and standardized tests of various cognitive areas. The SNSB includes tests that assess attention, language, praxis, calculation, visuo-constructive function, memory (verbal and visual), and frontal/executive functions and provide numeric scores in most items. Among them, digit span (forward and backward), calculation, ideomotor praxis, the Korean version of the Boston Naming Test (K-BNT), the Rey-Osterrieth Complex Figure Test (RCFT), the Seoul Verbal Learning Test (SVLT) (immediate and a 20-min delayed recall trial for the 12 items), fist edge arm test, alternating hand movement test, alternating square test, Luria test, contrasting program test, go-no-go test, test of semantic fluency and letter-phonemic fluency (the Controlled Oral Word Association Test, or COWAT), Stroop test (Color Word Stroop Test or CWST) were adopted for this research. All study subjects underwent neuropsychological tests using the same protocol. When tests could not be accomplished for any reason, we repeated these missed tests another day by the same examiner. Nevertheless, if these tests were left in blank, then we distinguished between missing values due to cognitive dysfunctions (or delusion) and missing values due to other reasons (e.g. communication problem, medical illness etc.). Only missing values due to cognitive dysfunctions (or delusion) were subjects of this study.

Statistical analysis

First, the baseline characteristics of the AD patients with MIS, paranoid delusion, and without delusions were assessed by one-way ANOVA tests and chi-square tests. Second, the patterns of missing values in each neuropsychological test were assessed and computed by Chi-square test among study groups for significance using the two tailed tests.

For all test scores, unadjusted means were computed. Next, while we replaced each missing value by series mean in non-significant neuropsychological test items among study groups, we replaced each missing value by the worst score found on that test in significantly different test items among study groups. After this adjustment, we computed means of the adjusted scores.

Statistical analyses were performed with the SPSS version 18.0 (SPSS, Inc, Chicago, IL, USA), and a significance level of 0.05 was set for analyses.

RESULTS

Characteristics of the patients

The study included 26 AD patients with MIS, 25 AD patients with paranoid delusions, and the remaining 31 AD patients with non-delusion. The AD with MIS showed significantly lower scores for Barthel index compared to other groups. Though education level and CDR of AD with MIS was higher than other groups, there was no statistical difference among study subjects (Table 1). Age, dementia onset age, duration, and GDS were not significantly different among study subjects.

Number of missing values in study subjects

Some patients were unable to perform particular neuropsychological tests and the numbers of missing values according to study subjects were shown in Table 2. According to study groups and neurological test items, there were various numbers of missing values from 0% to 34.8%. Contrast and GO-no-go tests showed significantly more missing values in

Table 1: Demographic data for drug-naïve AD patients with MIS, paranoid delusions and non-delusion(mean ±standard deviation).

	MIS	Paranoid	Non-delusion	p-value†
Numbers(female)	26(15)	25(16)	31(20)	0.101
Age (year)	74.0±8.0	77.7±5.5	71.8±6.8	0.116
Onset age (year)	70.7±7.7	75.2±7.7	68.6±8.6	0.383
Duration (month)	39.4±20.7	37.4±30.9	41.1±37.8	0.193
Education	8.5±6.6	7.7±3.6	7.3±5.1	0.089
K-MMSE	16.0±4.9	16.9±3.2	16.6±3.0	0.561
CDR	1.7±0.8	1.4±0.7	1.5±0.5	0.085
Barthel	17.4±4.4	18.9±2.1	19.3±1.3	0.042
GDS	13.6±6.5	15.5±6.8	14.5±7.5	0.725

† One-way ANOVA test was done. MIS; misidentification syndrome, K-MMSE; Korean Mini-Mental State Examination, CDR; Clinical Dementia Rating Scale, GDS; Geriatric Depression Scale

patients with MIS than other group (Table 2). There were no statistical differences in the number of missing values in other neuropsychological tests.

Differences of neuropsychological tests among non-delusion, paranoid delusion and MIS in observed and adjusted data

Table 3 shows the differences of each neuropsychological test among MIS, paranoid delusion and non-delusion in the observed data. Before missing value adjustments, AD patients with MIS showed significantly lower scores in SVLT immediate recall than other groups, and showed significantly lower scores in RCFT copy, COWAT animal, COWAT supermarket, CWST color than paranoid groups. The paranoid delusions group showed significantly higher scores in COWAT phonemic than other groups. After data adjustment, AD patients with MIS additionally showed significantly lower scores in contrast program than paranoid delusions groups, and lower scores in go/no-go tests compared to other groups (Table 4).

DISCUSSION

Among various types of delusions, MIS showed characteristic symptoms. They usually showed monothematic and simple delusional contents compared to other delusions. Though this symptom occur with various neurologic and psychiatric conditions, these phenomena have been particularly seen in certain form of neurodegenerative condition such as AD and DLBD which is characterized by pronounced memory and visuospatial deficits.

There is considerable controversy over whether AD patients with MIS showed disproportionate specific cognitive dysfunctions relative to the observed global cognitive dysfunction. This study aimed to assess the neuropsychological characteristics of AD patients with MIS compared to AD patients with paranoid delusions and without delusion.

Previous studies reported that patients with delusions were significantly lower scores on frontal function [18] and misidentification were significantly lower scores on the RCFT copy, RCFT immediate recall, and verbal fluency from non-psychotics, whereas paranoid group did not differ significantly from the non-psychotic on any cognitive measure [9]. However, the former study did not separately analyze the delusion subtypes and the latter study did not control global cognitive status such as CDR and MMSE.

To settle these methodological problems, we first subdivide the delusion types, and then identified the MIS group. Because MIS is relatively rare and occurs in more advanced stages of dementia than other groups, a control group (i.e, paranoid delusions and non-delusion) was selected in K-MMSE matched subjects.

MIS group usually appear in moderate to severe stage of dementia. And that time, cognitive function and attention of patients may be lower than patients with mild stage of dementia regardless of the presence of delusion and significant portion of neurological test items can be left unfinished. Though, specific missing neuropsychological test items can be closely correlated with poor performance for certain patients, there are few reports for missing patterns and missing value replacement analysis for patients with delusions.

We meticulously examined all neuropsychological test items to see whether certain tests were disproportionately left unfinished. Interestingly, most of neurological tests except

Table 2: Number of valid test, missing value due according to delusions subtypes and non-delusions.

Tests	MIS(26)		Paranoid(25)		Non-delusion(31)		p-value†
	Valid	Missing value(%)	Valid	Missing value(%)	Valid	Missing value(%)	
Digit forward	25	1(3.8)	23	2(8.0)	31	0(0)	0.284
Digit backward	23	3(11.5)	22	3(12.0)	31	0(0)	0.140
K-BNT	25	1(3.8)	24	1(4.0)	31	0(0)	0.536
Calculation	25	1(3.8)	23	2(8.0)	29	2(6.5)	0.821
Ideomotor praxis	25	1(3.8)	24	1(4.0)	30	1(3.2)	0.986
SVLT immediate recall	26	0(0)	25	0(0)	30	1(3.2)	0.435
SVLT delayed recall	26	0(0)	25	0(0)	30	1(3.2)	0.435
RCFT copy	25	1(3.8)	22	3(12.0)	27	4(12.9)	0.467
RCFT immediate copy	23	3(11.5)	21	4(16.0)	24	7(22.6)	0.309
RCFT delayed copy	23	3(11.5)	21	4(16.0)	24	7(22.6)	0.536
Contrasting‡	18	8(30.8)	23	2(8.0)	29	2(6.5)	0.019
Go-no-go‡	18	8(30.8)	23	2(8.0)	29	2(6.5)	0.019
Fist-edge-arm	25	1(3.8)	25	0(0)	30	1(3.2)	0.701
Alternating hand	25	1(3.8)	25	0(0)	30	1(3.2)	0.701
Alternating square	23	3(11.5)	23	2(8.0)	27	4(12.9)	0.981
Luria	25	1(3.8)	23	2(8.0)	28	3(9.7)	0.654
COWAT animal	25	1(3.8)	25	0(0)	30	1(3.2)	0.631
COWAT supermarket	25	1(3.8)	25	0(0)	30	1(3.2)	0.631
COWAT phonemic	21	5(23.8)	19	6(31.6)	24	7(22.6)	0.914
CWST word correct	21	5(23.8)	21	4(16.0)	23	8(34.8)	0.098
CWST color correct	21	5(23.8)	21	4(16.0)	23	8(34.8)	0.650

Table 3: Observed means difference among non-delusion, paranoid delusion and MIS.

	MIS	Paranoid	Non-delusion	p-value
Digit forward	4.4±1.4	4.4±1.1	4.1±0.9	0.422
Digit backward	2.6±1.1	2.2±1.3	2.3±1.0	0.540
K-BNT	25.0±11.8	25.7±11.3	23.5±8.1	0.716
Calculation	7.1±4.0	7.4±3.8	5.4±3.7	0.104
Ideomotor praxis	3.6±1.3	3.0±1.9	2.8±1.7	0.286
SVLT immediate recall†	7.3±5.0	11.7±4.5	10.6±5.0	0.004
SVLT delayed recall	0.7±2.0	1.0±2.3	1.0±2.0	0.792
RCFT copy‡	12.0±11.5	20.5±9.9	16.3±11.2	0.027
RCFT immediate copy	2.7±3.6	3.5±3.8	1.9±2.3	0.511
RCFT delayed copy	2.0±4.9	2.6±5.5	2.4±3.3	0.925
Contrasting	12.4±8.0	15.2±7.8	12.4±7.9	0.396
Go-no-go	7.5±6.4	11.9±7.6	9.5±8.0	0.176
Fist-edge-arm	0.2±0.4	0.3±0.5	0.2±0.4	0.675
Alternating hand	0.1±0.2	0.2±0.3	0.3±0.4	0.397
Alternating square	0.6±0.5	0.6±0.4	0.7±0.4	0.826
Luria	0.6±0.5	0.7±0.5	0.4±0.5	0.167
COWAT animal‡	6.7±3.3	8.9±5.0	7.7±3.7	0.047
COWAT supermarket‡	5.6±4.0	9.0±4.7	7.0±4.8	0.030
COWAT phonemic§	9.0±6.4	19.2±9.3	10.6±6.7	0.007
CWST word correct	91.2±33.1	93.8±28.1	101.9±14.1	0.530
CWST color correct‡	22.1±17.5	40.7±30.1	25.6±21.3	0.042

†Statistcial difference was found between MIS and other groups ‡Statitical difference was found between MIS and paranoid delusions § Statistcial difference was found between paranoid delusions and other groups MIS; misidentification syndrome, K-BNT; Korean version of the Boston Naming Test, SVLT; Seoul Verbal Learning Test, RCFT; Rey-Osterrieth Complex Figure Test, COWAT; Controlled Oral Word Association Test, CWST; Color Word Stroop Test

Table 4: Adjusted mean difference of contrasting and go/no-go test among study subjects (mean ±standard deviation).

	MIS	Paranoid	Non-delusion	p-value†
Contrast‡	8.6±7.8	15.2±8.7	12.4±8.3	0.045
Go-no-go§	5.2±6.4	11.8±8.0	9.9±8.1	0.025

† One-Way ANOVA test was done ‡ Statistical significance was found between paranoid delusion and MIS §Statistical significance was found between MIS and other groups.MIS; misidentification syndrome

contrast program and go/no-go tests did not have any statistical difference among study subjects and we only replaced the missing values in these tests with MIS by the lowest observed scores. Missing values due to other reasons were excluded from this study. Therefore, in our study replacing missing values due to delusion subtypes by the lowest scores can be justified.

In our study, MIS showed significantly lower scores in SVLT immediate recall compared to other groups, and RCFT copy, COWAT supermarket, COWAT phonemic, CWST color test compared to paranoid delusion group. And after missing value adjustment, contrast program and go/no-go tests showed additionally significantly lower scores compared to paranoid group and other groups.

Go/no-go tests are usually taken for investigating response inhibition, which is conditio sine qua non for executive function of humans. In this test, subjects should respond to a go stimulus, and halt their response to a no-go stimulus. To do this test, various cognitive functions, including stimulus-driven attention, error monitoring, top-down control processes, working memory, and response inhibition should be mobilized. Neuropsychological [19] and transcranial magnetic stimulation (TMS) [20] studies has suggested that the right ventrolateral prefrontal cortex (VLPFC) plays an important role in response inhibition, which is consistent with neuroimaging studies [21]. Another neuroimagning study reported that go/no go test additionally recruits right fronto-parietal networks, particularly in the posterior inferior frontal gyrus [22].

Our study suggested that frontal, right parietal, and left temporal dysfunctions were associated with MIS. Contrasts to patients with MIS, the patients with paranoid delusions were mostly statistically not different in neuropsychological test compared to patients with non-delusion.

In the past, delusions were just the archetypal signs of madness and the core feature of functional psychosis like schizophrenia. However, as the chance for seeing delusion rapidly increases due to the rapid growth of the elderly population and age-associated AD, the research for neurocognitive aspects and anatomic substrates of this characteristic delusion of MIS has been triggered.

Among various hypotheses to explain delusional contents and incorrigibility, two factor theory is a widely used hypothesis. In this hypothesis, triggering factor (perceptual defect) and verifying factor (error monitoring failure) is necessary conditions for delusion formation [23]. Previous study of MIS suggested the frontal and right parietal dysfunction may be anatomic substrates [9].

Our data may be in accordance with this suggestion. Additionally, considering MIS is more hampered in short form memory, visuospatial function and both frontal functions compared to paranoid group, we could suggest that different pathophysiological mechanism may exist between paranoid group and MIS groups.

However, this study had several limitations. First, this study is retrospective study and sample size is relatively small compared to the number of factors. Secondly, though we excluded the missing values due to other non-cognitive reason by other researcher, the possibility of false positive and negative cases are not completely ruled out. Thirdly, delusions were detected with the NPI, a questionnaire that determines the frequency and severity of the patient's symptoms by questioning a relative or caregiver. Hence, the patient's reported symptoms may be somewhat imprecise due to the relative or caregiver either forgetting or misrepresenting the actual symptoms. Finally, our study is a hospital-based study, and so it may not represent a real community.

In conclusion, our study show that MIS is disproportionately cognitive deficit suggesting left temporal, right parietal and both

frontal dysfunction(especially in right frontal). Considering neuropsychological differences between MIS and paranoid delusions, these symptoms may have different anatomic substrates. In a future study, higher number of drug-naïve patients and more specific tests that represent specific anatomical substrates may produce a better understanding for the biological pathophysiology of delusion subtypes.

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Cite this article

Kwak YT, Yang YS, Koo MS, Kwak SG (2013) The Neuropsychological Characteristics of Misidentification Syndrome. J Neurol Transl Neurosci 1: 1008.