Physical Disabilities Related to the Depressive Mental States of Japanese Patients with Subacute Myelo-optico-neuropathy

Tetsuro Konishi

Abstract:

Objective  The aim of this study was to clarify the clinical conditions related to the depressive mental states in Japanese patients with subacute myelo-optico-neuropathy (SMON), caused by clioquinol intoxication more than 40 years previously.

Methods  The changes in the mental states with aging were investigated in 25 Japanese SMON patients (mean age: 77.2 years old, range: 53-90) using a Japanese version of the Zung Self-rating Depression Scale (J-SDS) questionnaires with supportive interviews by the clinical psychotherapist and medical checkup records. These mental and medical examinations were repeated more than twice within 2 to 11 years’ interval. The J-SDS questionnaires were also examined in 25 age-matched non-SMON elderly people.

Results  The total J-SDS scores of most of the SMON patients decreased with age without significant changes in the mean Barthel index scores during this study period. The mean J-SDS scores at the first and latest studies were significantly higher than in the age-matched healthy elderly people. The total J-SDS scores of the latest study were significantly correlated with the degree of physical disability, such as the inverse total Barthel index scores, severity of SMON or gait disturbance, but not with the age.

Conclusion  The total J-SDS scores of most of the SMON patients tended to decrease with age. Repeating mental supportive interviews and medical examinations by experts helped to improve the depressive mental state and revealed close relationship between the mental state and the physical disabilities of the SMON patients.

Key words: subacute myelo-optico-neuropathy (SMON), Japanese version of Zung Self-rating Depression Scale (J-SDS), depressive mental state, Barthel index, clinical psychotherapist, clioquinol intoxication

Introduction

Subacute myelo-optico-neuropathy (SMON) is a disease caused by clioquinol intoxication, characterized by the subacute onset of sensory and motor disturbance in the lower extremities, with visual impairment following abdominal symptoms, mainly occurring during 1950s to 1960s in Japan (1). After the sale of drugs containing clioquinol was banned in 1970, a sharp decrease in the number of new SMON patients was observed in Japan. It is estimated that the total number of SMON patients reached nearly 10,000 by the end of 1970 (1) and decreased to 1,748 in 2013 (2). The mean age of SMON patients was over 80 in 2016 (3). Almost all SMON patients suffer from the sequelae of clioquinol intoxication experienced around 40 years earlier, and various kinds of mental and physical complications as observed in these elderly individuals (3).

The prevalence of major depressive disorder in SMON patients, estimated by a structured interview and using Beck’s depression inventory (BDI) questionnaires, was seven times more frequent than in age-matched non-SMON elderly
The simultaneous supportive interviews by the clinical psychologist more than 40 indicate a depressive mental state (9). Items representing depressive mood, graded on a scale of 1 to 4. The total J-SDS scores range between 20 and 80, and a score more than 40 indicate a depressive mental state (9). The simultaneous supportive interviews by the clinical psychologist included listening to the patient to share problems about their physical and life conditions and asking how the patient spent their leisure time. The physical condition including the clinical symptoms of SMON, was evaluated repeatedly using the screening medical checkup records, established by the SMON Research Committee in Japan. These records were examined by neurologists who also had a good understanding of the mental complications of SMON. The degree of peculiar dysesthesia and visual impairment and the gait scores were graded as described previously (8), and the aggravation of each symptom was represented as a smaller number. In each patient, the total score of the Barthel index (10), which represents the activity of daily life, was calculated as the sum of 10 questionnaires (total score: 100), with a smaller number indicating poorer daily life activity. All SMON patients and non-SMON elderly subjects in this study underwent a mini-mental state examination (11), with a score of >24 points indicating a normal cognitive function.

None of the patients were treated with anti-depressants nor suffered from additional neurological disorders, such as dementia and cerebrovascular disorders, except one patient with mild Parkinson disease (Hoehn-Yahr stage 2), nor from malignancy during the study period. This study was approved by the ethics committee of Gakusai Hospital, and each patient gave their informed consent.

The results of the J-SDS questionnaires and the medical checkup records of the first and latest mental and medical examinations were used for the statistical analysis using Spearman’s rank correlation, Student’s t-test or Fisher’s exact test. A value of p<0.05 was considered to indicate statistical significance.

**Results**

**J-SDS changes with age**

The first total J-SDS scores of 25 SMON patients were 43.8±11.9 (mean ± SD, range: 29-67), and the latest total J-SDS scores of the same patients were 40.4±9.4 (range: 23-60) (Table 1). The mean total J-SDS score decreased in the people at 2008 (4). The ratio of SMON patients whose total BDI scores exceeded 25 points and who suffered from severe depressive mood was significantly higher than that of age-matched non-SMON elderly people (4). A previous study using the Japanese version (5) of the Zung Self-rating Depression Scale (J-SDS) (6) questionnaires showed that the degree of depressive mental state in SMON patients was more severe than in patients with various intractable nervous diseases (7). The depressive mental state of some SMON patients is aggravated with age, especially in patients whose physical disabilities are too severe to allow them to walk freely or go outside by themselves (8).

The aim of this study was to clarify the clinical conditions related to the depressive mental state of SMON patients by repeating mental and medical examinations.

**Materials and Methods**

The mental state and physical condition were simultaneously evaluated in 8 male and 17 female Japanese SMON patients (mean age ± standard deviation (SD): 70.7±8.3 years old, range: 53-90 years old) living in Kyoto Prefecture using the J-SDS questionnaire (5) and the screening medical checkup records. The frequency of mental and medical examinations of each patient was once every few years, and the mean interval between the first and latest examinations was 6.5±2.2 years (range: 2-11 years). During this study period, these examinations were repeated more than twice for each patient (mean time ± SD: 4.0±1.5, range: 2-7 times) with interviews by the same clinical psychotherapist, who had a good understanding of SMON. The J-SDS questionnaires were also administered to 25 age-matched elderly people (16 men, 9 women, mean age ± SD: 74.6±7.3 years old, range: 56-93 years old) who had visited the hospital as relatives of outpatients, excluding those with intractable nervous disorders.

The total J-SDS scores are the sum of each score of 20 items representing depressive mood, graded on a scale of 1 to 4. The total J-SDS scores range between 20 and 80, and a score more than 40 indicate a depressive mental state (9). The mean interval between the first and latest examinations was 6.5±2.2 years (range: 2-11 years). During this study period, these examinations were repeated more than twice for each patient (mean time ± SD: 4.0±1.5, range: 2-7 times).

### Table 1. Mean Ages and Mean J-SDS Scores of the First and Latest Studies of the 25 SMON Patients and of the 25 Non-SMON Elderly Subjects.

| subjects          | age (mean±SD) | J-SDS score (mean±SD) | Ratio>40 points (percentage) | Barthel index score (mean±SD) |
|------------------|---------------|-----------------------|-----------------------------|-------------------------------|
| first study      | 70.7±8.3      | 43.8±11.9**           | 15/25 (60)**                | 87.4±15.9                     |
| latest study     | 77.2±8.3      | 40.4±9.4*            | 13/25 (52)*                | 86.2±16.0                     |
| non-SMON         | 74.6±7.3      | 35.0±7.1             | 5/25 (20)                  |                               |

The mean J-SDS scores of the first and latest studies of the SMON patients were not significantly different (p=0.136 by Student’s t-test) but were significantly higher than the mean score of the non-SMON elderly subjects. The percentages indicate those whose J-SDS scores exceeded 40 points in each group. The mean J-SDS scores and the ratios of the SMON patients whose J-SDS scores exceeded 40 points were compared to those of non-SMON elderly subjects by Student’s t-test and Fischer’s exact test, respectively. The means and SD of Barthel index scores of the first and the latest studies are shown in the right-most column. *: p<0.05, **: p<0.01
latest study, but the difference in the mean values between the first and the latest study was not significant (p=0.136 by Student’s t-test). The latest total J-SDS scores of 6 patients increased more than 10% over the first ones. The mean total J-SDS scores of the first and latest studies were significantly higher than in the age-matched elderly subjects, in whom the mean ± SD of the total J-SDS scores was 35.0±7.1 (Table 1). The mean ages of these 3 groups were not significantly different (mean age ± SD in the first study: 70.7±8.3 years old, latest study: 77.2±8.3 years old, age-matched elderly subjects: 74.6±7.3 years old). Five (20%) of the 25 age-matched elderly subjects had a total J-SDS score exceeding 40, which indicates a depressive mental state (9), and more than a half of the SMON patients had scores over 40 items of the J-SDS questionnaires in both the first and latest studies of the SMON patients (depressed affects, irritability, suicidal ruminations and dissatisfaction) were significantly worse than in the non-SMON elderly subjects (Table 2). On comparing the first and latest studies of the SMON patients, fatigue improved, and libido decreased over time. Although the hopelessness improved to a non-significant degree, the degree of hopelessness was significantly smaller in the latest study for SMON subjects than in the non-SMON elderly subjects. Among the items with significant differences from the non-SMON elderly subjects, the depressed affect, the irritability and the suicidal rumination were almost unchanged, with t-values between the first and latest study of ±1.000 (Table 2).

### Correlation between the total J-SDS scores and the clinical parameters

Among the clinical parameters of the SMON patients, the age, onset age, Barthel index and degree of severity of SMON symptoms, gait disturbance, going outdoors, visual impairment and dysesthesia of legs were selected from the medical checkup records for the analysis. These clinical conditions mainly represent the neurological sequelae of the clioquinol intoxication experienced more than 40 years earlier. The correlations between the total J-SDS scores and these clinical parameters were evaluated based on Spearman’s rho (Table 2).

### Table 2. Results of Student’s t-test for the 20 Items of the J-SDS Questionnaires for the First Study of the SMON Patients Versus the Non-SMON Elderly Subjects (Second Column from the Left), for the Latest Study Versus the Non-SMON Elderly Subjects (Third Column from the Left) and for the Latest and First Studies (Fourth Column from the Left).

| 20 items of J-SDS questionnaires | t-values between first study and non-SMON | t-values between latest study and non-SMON | t-values between latest and first study |
|---------------------------------|------------------------------------------|------------------------------------------|--------------------------------------|
| depressed affect                 | 2.799**                                  | 4.249**                                  | 0.514                                |
| diurnal variation                | 2.511*                                   | 1.274                                   | -1.5398                              |
| crying spells                    | 1.066                                    | 1.992                                   | 0.891                                |
| sleep disturbance                | 2.543*                                   | 1.940                                   | -0.775                               |
| decreased appetite               | -0.842                                   | -1.023                                  | -0.166                               |
| decreased libido                 | -1.585                                   | 2.103*                                  | 3.980**                              |
| weight loss                      | 0.741                                    | 0.985                                   | 0.146                                |
| constipation                     | 0.957                                    | 1.012                                   | 0.000                                |
| tachycardia                      | 1.922                                    | 0.719                                   | -1.778                               |
| fatigue                          | 1.678                                    | -0.831                                  | -2.971**                             |
| confusion                        | 1.111                                    | -0.267                                  | -1.622                               |
| psychomotor retardation          | 0.960                                    | -0.487                                  | -1.568                               |
| psychomotor agitation            | 1.129                                    | 1.832                                   | 0.659                                |
| hopelessness                     | -0.793                                   | -2.354*                                 | -1.953                               |
| irritability                     | 2.938**                                  | 2.938**                                 | 0.000                                |
| indecisiveness                   | 1.224                                    | -0.132                                  | -1.901                               |
| personal devaluation             | 1.264                                    | 0.461                                   | -1.000                               |
| emptiness                        | 2.528*                                   | 1.756                                   | -1.319                               |
| suicidal ruminations             | 2.350*                                   | 2.058*                                  | -0.310                               |
| dissatisfaction                  | 3.603**                                  | 2.294*                                  | -1.200                               |

Positivity indicates aggravation, and negativity indicates improvement compared with the latter subjects. *: p<0.05, **: p<0.01
The observed lack of a correlation between the total J-SDS scores and the age in both first and latest studies of SMON patients may be due to the patients’ physical disabilities related to the neurological sequelae of the clioquinol intoxication. The improvement in the fatigue in the latest study was not due to an improvement in the patients’ physical condition, since the Barthel index scores tended to decrease with age. The improvement in the hopelessness in the latest study also contributed to the improvement in the depressive mental state of SMON patients. The degree of depressed affects, irritability, suicidal rumination and dissatisfaction of the J-SDS questionnaires was markedly worse in both studies among SMON patients than in age-matched non-SMON elderly subjects, contributing to the higher total J-SDS scores of the SMON patients than age-matched non-SMON elderly subjects.

An interesting finding in this study was the presence of a significant difference in the depression rating in the total J-SDS scores and physical disabilities in the latest study but not in the first study. Since the improvement in the depression by treatments was already known to be correlated with the decrease in the total J-SDS scores (5, 6), the decrease in the total J-SDS scores of the latest study among SMON patients indicated an improvement of the depressive mental state of these SMON patients, reflecting the improvement in the fatigue score on the J-SDS questionnaire. The lack of a significant difference in the mean total J-SDS scores between the first and latest studies of the SMON patients was due to the presence of SMON patients, whose total J-SDS scores increased from the first study to the latest study. The physical disabilities, especially gait disturbance, of these aggravated patients tended to be too severe to allow them to freely go outside, even when using wheelchairs, which reflected less opportunity to engage in social activities, as previously reported (8). Why the depressive mental state of most of the SMON patients improved with age without any antidepressant medication was not clear in this study. It may have been due to the repeated engagement and sharing their individual mental problems with experts familiar with their situation, especially neurologists and the clinical psychotherapist who understood SMON well.

A study using SDS questionnaires in elderly persons living in the community found that female gender, having activity of daily life and having an emotional support network and a good relationship with friends and relatives were important independent factors contributing to a depressive mental state (12). It is therefore conceivable that repeated medical examinations and supportive interviews with experts functioned as emotional support for SMON patients, helping ameliorate their depressive mental state except for the depressant medication was not clear in this study. It may also contributed to the improvement in the depressive mental state of SMON patients. The degree of depressed affects, irritability, suicidal rumination and dissatisfaction of the J-SDS questionnaires was markedly worse in both studies among SMON patients than in age-matched non-SMON elderly subjects, contributing to the higher total J-SDS scores of the SMON patients than age-matched non-SMON elderly subjects.

### Discussion

More than half of SMON patients in our study had J-SDS scores over 40 points, findings that were comparable to those of a previous study (4) in which BDI questionnaires were used to clarify the increased prevalence of major depressive disorder in SMON patients. This study also confirmed the previous finding that the depressive mental state of the SMON patients was still more severe than in age-matched non-SMON elderly subjects more than 40 years after clioquinol intoxication. The other significant finding of this study was that repeated mental and medical examinations by experts improved the depressive mental state to some extent and disclosed a close relationship between the depressive mental state and patients’ physical disabilities related to the neurological sequelae of the clioquinol intoxication.
SMON patients and the improvement in the depressive mental state with age may have been due to the exclusion of demented patients from this study. In elderly populations in Japan, the rate of depression coexisting with dementia increases with age, while the rate of depression without dementia does not change markedly in any age groups (13). The exclusion of demented persons from this study might have resulted in the slightly lower mean J-SDS score (35.0) for age-matched non-SMON elderly people in this study compared with the mean score (36.3-37.3) obtained from similar elderly people in Japan (13).

The findings from the present study indicate that the physical disabilities induced by the neurological sequelae of clioquinol intoxication, represented by a low Barthel index, severity of SMON and gait disturbance, influenced the depressive mental state of SMON patients. Many studies have already explored depression in the elderly populations, in whom physical health impairment is a cause of a depressive mental state (12, 14, 15). Physical disabilities might also represent a barrier to participating in social activities. In a previous study, the maintenance of social activities via public support was found to be an important factor for coping with a depressive mental state among SMON patients, especially those who could no longer walk independently or go outside freely without aid (8). To further ameliorate the depressive mental state of SMON patients, sufficient social support from the Japanese Government is necessary, especially for those who are suffering from severe physical disabilities. Strategies for coping with the depressive mental state of SMON patients with the help of experts considering the mental and physical backgrounds of individual patients may also prove useful for relieving the depressive symptoms in patients suffering from other intractable nervous diseases (7).

The author states that he has no Conflict of Interest (COI).

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References

1. Sobue I. Clinical aspects of subacute myelo-optico-neuropathy (SMON). In: Intoxications of the Nervous System: Part 2. Handbook of Clinical Neurology, vol. 37. Vinken PJ, Bruyn GW, Eds. North-Holland, Amsterdam, 1979: 115-139.
2. Konagaya M. SMON: Toxicity of clioquinol and the status quo. Brain Nerve 67: 49-62, 2015 (in Japanese, Abstract in English).
3. Konagaya M. Present conditions of Japanese SMON patients from the annual medical checkup in 2016. In: Annual report of SMON Research Committee in 2017. Konagaya M, Ed. SMON Research Committee supported by the Ministry of Health, Labor and Welfare of Japan, Nagoya, 2017: 27-49 (in Japanese).
4. Konishi T, Hayashi K, Hayashi M, et al. Depression in patients with subacute myelo-optico-neuropathy (SMON). Intern Med 47: 2127-2131, 2008.
5. Fukuda K, Kobayashi S. Japanese version of SDS (self-rating depression scale). Augmented version. Sankyobo, Kyoto, 2011 (in Japanese).
6. Zung WWK. A self-rating depression scale. Arch Gen Psychiatry 12: 63-70, 1965.
7. Konishi T, Fujita M, Hayashi K. Depressive mental states in SMON patients. In comparison with various intractable nervous diseases and healthy people. Kyoto Igakukai Zasshi (J Kyoto Medical Association) 64: 75-79, 2017 (in Japanese).
8. Konishi T, Hayashi K, Sugiyama H. Aggravation of the depressive mental states with aging in Japanese patients with subacute myelo-optico-neuropathy (SMON). Intern Med 56: 2119-2123, 2017.
9. Zung WWK. From art to science. The diagnosis and treatment of depression. Arch Gen Psychiatry 29: 328-337, 1973.
10. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Md State Med J 14: 61-65, 1965.
11. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 40: 922-935, 1992.
12. Kawamoto R, Doi T, Yamada A, et al. A study of depressive state and background factors in community-dwelling older persons. Nihon Rohnen Igakukai Zasshi (J Jpn J Geriatrics) 36: 703-710, 1999 (in Japanese, Abstract in English).
13. Komahashi T, Ohmori K, Nakano T, et al. Epidemiological survey of dementia and depression among the aged living in the community in Japan. Jpn J Psychiatry Neurol 48: 517-526, 1994.
14. Blazer D, Williams CD. Epidemiology of dysphoria and depression in an elderly population. Am J Psychiatry 137: 439-444, 1980.
15. Fukuda H, Kida K, Kimura Y, et al. Well-being and depression in residents of a provincial city 65 years old or older. Nihon Kohsu Eisei Zasshi (J Jpn J Public Health) 49: 97-105, 2002 (in Japanese, Abstract in English).

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