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Relationship between exploratory eye movements and clinical course in schizophrenic patients

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Abstract Exploratory eye movements are psychophysiological indicators of schizophrenia as well as smooth pursuit eye movements. To investigate whether these eye movements change in accordance with the clinical course of the condition in schizophrenia, exploratory eye movements (number of eye fixations, mean eye scanning length, responsive search score, evaluation of reproduced Fig. 1 and 2) of 28 schizophrenic patients were evaluated in repeat test design, conducted an average of 8 months apart. Subjects were first-medicated schizophrenics, half were outpatients and the remaining half were inpatients at the Neuropsychiatry ward of Tokyo Medical and Dental University Hospital. Exploratory eye movement patterns did not improve despite an improvement in clinical symptoms of schizophrenia. This result and those of previous studies of the exploratory eye movements of schizophrenic patients' families suggest that exploratory eye movements reflect a schizophrenic vulnerability marker. Furthermore, decreased mean eye scanning length (MESL) values were observed in subjects who showed unimproved symptoms, particularly negative symptoms over an extended period of time. The result suggests that a decrease in the MESL value may be the most sensitive indicator in the development of chronicity in schizophrenia.

Key words Exploratory eye movements · Schizophrenia · Vulnerability marker · Clinical course · Chronicity

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Introduction

Exploratory eye movements are psychophysiological indicators of schizophrenia as well as smooth pursuit eye movements. Compared with normal healthy subjects, schizophrenic patients exhibit limited exploratory eye movements when they are shown stationary horizontal S-shaped figures (Moriya et al., 1972; Kojima et al., 1989, 1990; Matsushima et al., 1992). Furthermore, the pattern of eye movements for schizophrenic patients differs from that exhibited by other psychiatric patients (Kojima et al., 1986, 1992) and eye movements do not differ significantly prior to and after medication (Kojima et al., 1990). Therefore this limited pattern of exploratory eye movements is considered to be specific to schizophrenia (Matsushima et al., 1998). In addition, because this pattern can also be seen in the parents of schizophrenic patients (Moriya et al., 1979; Xia et al., 1996), eye movement patterns are considered to be a vulnerability marker of schizophrenia.

Kojima et al. (1990) compared the exploratory eye movements of schizophrenic patients in acute, chronic and remitted stages of schizophrenia. Although all patient groups exhibited eye movements that were fewer and more limited than those of healthy subjects, a significant difference in mean eye scanning length was observed between the chronic group and the remitted group. These results indicated that exploratory eye movements are not only disease-specific markers but are also state-dependent. However, they did not observe subjects over time and, thus, this conclusion remained under active investigation.

Therefore, the present study investigated whether exploratory eye movements of schizophrenic patients were influenced by changes in symptoms or not in repeat test design over a certain period.

Methods

Subjects

The subjects were 28 schizophrenic patients (19 males and 9 females; age range 17–54, mean age 30.5 ± 9.7 years old (± S. D.)).who were diagnosed at the Tokyo Medical and Dental University Hospital using DSM-IV criteria (American Psychiatric Association, 1994). All patients were first-medicated schizophrenics including disorganized type schizophrenics showing long-term illness. They consisted of 24 first-episode schizophrenics and 4 second-episode schizophrenics. Mean duration of illness was 4.2 (±7.0) years (range 0.5–26 years). Patients were classified by subtype using DSM-IV criteria: paranoid type, 18; disorganized type, 7; undifferentiated type, 2; and catatonic type, 1. Fourteen of the 28 patients were newly admitted to the hospital and the remaining 14 were treated as outpatients. Twenty-nine age-matched healthy controls (22 males and 7 females; age 29.9 ± 5.7 years) acted as a control group (Mann-Whitney U test). Screening determined the absence of psychiatric illness in controls and in their first-degree relatives.

All 28 patients and 7 (5 males and 2 females) of the above-mentioned healthy control group underwent an exploratory eye movement retest six months or more after the initial test (average duration between both tests was 8.3 ± 3.9 months). To diagnose a patient as having a first episode, the patient must exhibit "6 months or more of continuous signs of a disease existing" according to DSM-IV criteria. This criterion determined the minimum duration period of 6 months between the initial test and retest. Furthermore, this delay between tests minimized the learning effect, which was necessary in order to determine whether chronicity of the disease influenced exploratory eye movements. "Chronicity" refers to not only the persistence of negative symptoms but a variety of factors including disorganization of personality, deterioration of negative symptoms, and resistance to medication. At the time of the initial test, 20 patients were receiving neuroleptic medication at the equivalent dose of 332.2 ± 491.1 mg of chlorpromazine a day (Davis, 1976) and at 310.5 ± 337.5 mg per day at the time of the retest. Eight of the 20 patients were not administered medication upon initial examination. All 28 patients were receiving medication at retesting. The amount of medication administered did not differ significantly between the time of the initial and repeat tests (Mann-Whitney U test).

Symptoms of all patients were evaluated at the time of each test using the Brief Psychiatric Rating Scale (BPRS, Overall et al., 1962). Point values for positive and negative symptoms were determined according to Tandon et al. (1992); the positive symptom value is represented by the accumulated BPRS values for conceptual disorganization, suspiciousness, hallucinatory behaviour and unusual thought content, whereas negative symptom value is comprised of the accumulated values for emotional withdrawal, motor retardation and blunted affect.

Patients were divided into two groups according to whether their symptoms improved (improved group) or not (unchanged group) using the following formula:

$$[\text{BPRS}(2) - \text{BPRS}(1)] \text{ divided by } \text{BPRS}(1)$$

where BPRS(1) is the total score recorded an the BPRS upon initial testing and BPRS(2) is the total score recorded at retesting. Consequently, patients having values of –0.2 or below (Borison et al., 1992, used this 20 % indicator as a responder) were placed in the improved group (15 subjects; 11 males and 4 females; 10 paranoid types, 3 disorganized types, 1 catatonic type and 1 undifferentiated type). The mean BPRS(1) and BPRS(2) scores in the improved group were 40.3 ± 7.1 and 26.4 ± 5.8 respectively. The mean positive symptom value which was 12.3 ± 4.1 in the initial test declined to 5.6 ± 1.8 in the repeat lest. The mean negative symptom value which was 9.1 ± 4.6 in the initial test also declined to 6.6 ± 3.3 in the repeat test. Those with values above –0.2 were placed in the unchanged group (13 subjects; 8 males and 5 females; 8 paranoid types, 4 disorganized types and 1 undifferentiated type). The mean BPRS(1) and BPRS(2) scores in the unchanged group were 36.3 ± 7.3 and 37.0 ± 7.5 respectively. The mean positive symptom value which was 9.8 ± 4.4 in the initial test went to 9.2 ± 3.8 in the repeat test. The mean negative symptom value which was 7.3 ± 3.5 in the initial test slightly increase to 8.9 ± 3.7 in the repeat test. No significant statistical differences in BPRS scores and daily dosage of chlorpromazine equivalent were found between the two groups upon initial testing (Mann-Whitney U test). Furthermore, there was no significant difference between the ratio of outpatients and inpatients in the two groups (chi-squared test).

Procedure

The method used in this research is according to Kojima et al. (1992). All subjects received an explanation of the nature and aims of the tests and informed consent was received prior to this study. A nac-V type eye mark recorder was placed an the subjects head during the test, and three S-shaped figures were viewed consecutively following the procedure described below. The subject's eye movements were recorded an video tape.

1. Each subject was shown an original S-shaped target figure for 15 seconds (memory task) and then immediately instructed to draw the figure from memory.
2. The subject was then shown the target figure and two other slightly different figures for 15 seconds each. The subject was instructed to look at each figure, compare it with his / her memory of the target figure, and answer the question, "Are there any differences between this figure and the target figure?" Following this response, while still viewing the figure, the subject was asked again, "Are there any other differences?" This question was repeated until the subject stated that there were no differences present (comparison task).
3. The subject was then shown the original figure again and instructed to look at it carefully in order to draw it again. Finally, the subject was asked to draw the target figure from memory a second time.

Measurements

Video data were analyzed according to the three indices. Following the completion of the memory task, measurements of the two elemental indices of eye fixation points were taken: number of eye fixations (NEF) and mean eye scanning length (MESL). Upon completion of the memory task, the subject's responsive eye movements were studied for a five-second period following the question, "Are there any other differences?" in the comparison task. The number of sections on which the subject fixed his / her eyes once or more was calculated and constituted the responsive search score (RSS).

The figures drawn by the subject in steps 1 and 3 were each evaluated using a standard scale (evaluation of reproduced figure (ERF–1) and ERF–2).

Statistical analysis

The Mann-Whitney U test determined statistical significance between subjects and controls and between the initial test and repeat test.

Results

Comparison of exploratory eye movements in schizophrenic patients and normal controls upon initial testing

Values for the five indices of exploratory eye movements of patients compared to normal controls were NEF (patients 33.4 ± 6.0 vs. normal controls 39.6 ± 6.5, $p < 0.01$), MESL (17.1 ± 3.3 cm vs. 19.2 ± 3.4 cm, $p < 0.05$), RSS (8.7 ± 1.4 vs. 10.3 ± 1.8, $p < 0.01$) ERF–1 (4.5 ± 1.4 vs. 5.5 ± 1.2, $p < 0.05$) and ERF–2 (5.5 ± 1.0 vs. 6.2 ± 1.0, $p < 0.01$). All five indices differed significantly between the patient group and the normal control group. In the memory task, patients had fewer fixations and a smaller range of movement compared to normal controls. Furthermore, patients showed more limited responsive eye movements during the comparison task, and they drew less accurate figures from memory.

Comparison of eye movements upon the initial and repeat test

Normal controls: Results of the initial and repeat test are presented in Tab. 1. The controls showed no change in the five eye movement indices between the initial test and retest, indicating that the influence of the learning effect on eye movements examined is negligible over a period of more than six months and that the original results of the test are reproducible.

Patients: As seen in Tab. 2, the MESL value differed significantly between the initial and repeat test ($p < 0.05$). Statistical tendency was found in recorded values of RSS ($p < 0.1$). No significant difference was found between the initial and retest scores for NEF and the drawing exercise. BPRS values, referring to mental symptoms, were lower at the time of the retest, indicating that the patients' psychopathological condition had improved during psychiatric therapy.

Table 1 Comparison between initial and repeat test scores in 7 controls

	Initial test	Repeat test
NEF	42.1±5.4	42.1±6.7
MESL (cm)	19.3±3.6	19.1±4.0
RSS	10.0±1.2	9.9±1.3
ERF-1	5.6±0.8	6.0±0.7
ERF-2	6.0±1.0	5.9±1.0

All five eye movement indices showed no significant change using the Mann-Whitney U test.
NEF number of eye fixations, *MESL* mean eye Scanning length, *RSS* responsive search score, *ERF-1* evaluation of reproduced figure-1, *ERF-2* evaluation of reproduced figure-2

Table 2 Comparison between initial and repeat test scores in 28 schizophrenic subjects

	Initial test	Repeat test
NEF	33.4±6.0	30.8±6.8
MESL (cm)	17.1±3.3	14.6±3.4*
RSS	80.7±1.4	7.9±1.7***
ERF-1	40.6±1.4	40.9±1.2
ERF-2	5.5±1.0	5.2±1.3
BPRS total score	38.5±7.4	31.3±8.4**

* There was a significant ($p < 0.05$) difference between the initial and repeat test using Mann-Whitney U test.
** There was a significant ($p < 0.01$) difference between the initial and repeat test using Mann-Whitney U test.
*** There was a tendency ($p < 0.1$) between the initial and repeat test using Mann-Whitney U test
NEF number of eye fixations, *MESL* mean eye scanning length, *RSS* responsive search score, *ERF-1* evaluation of reproduced figure-1, *ERF-2* evaluation of reproduced figure-2

Comparison between improved and unchanged subjects

Improved group: Changes in exploratory eye movements between the initial and repeat test for the 15 subjects in the improved group are shown in Fig. 1 through 5. Despite an incomplete remission of symptoms, the exploratory eye movements barely changed. The change in mental symptoms demonstrated by the improved group were reflected in improvements in both positive and negative symptoms between the initial and repeat test.

Unchanged Group: Changes in eye movements between the initial and repeat test for the 13 subjects in the unchanged group are also shown in Fig. 1 through 5. MESL value recorded at the retest was significantly shorter ($p < 0.05$) than those upon initial testing. Furthermore, no significant change in mental symptoms

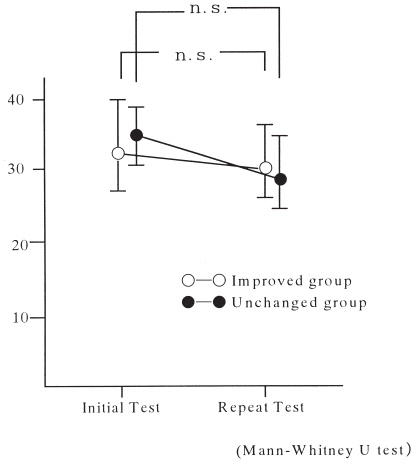

Fig. 1 Comparison of number of eye fixations in 15 improved subjects and 13 unchanged subjects between the initial test and repeat test. Circles and bars show median ± quarters. No significant change was observed between the tests in either group.

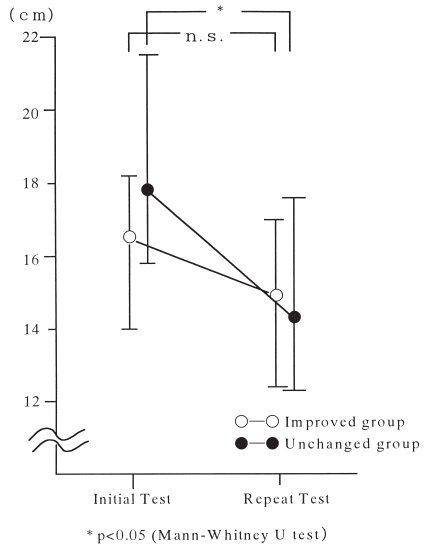

Fig. 2 Comparison of mean eye scanning length in 15 improved subjects and 13 unchanged subjects between the initial test and repeat test. Circles and bars show median ± quarters. A significant ($p < 0.05$) difference was observed between the initial and repeat test in the unchanged group.

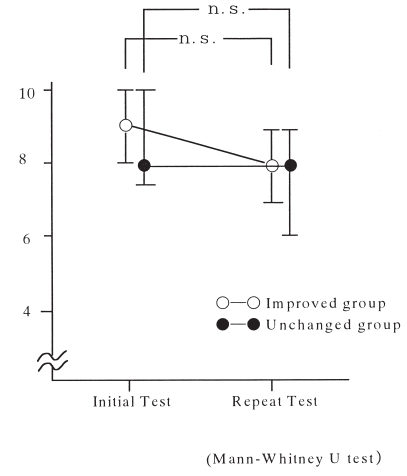

Fig 3 Comparison of responsive search score in 15 improved subjects and 13 unchanged subjects between the initial test and repeat test. Circles and bars show median ± quarters. No significant change was observed between the tests in either group.

was found between the initial and repeat test. Mild positive and negative symptoms persisted.

Comparison between paranoid type and non-paranoid type subjects

A comparison of NEF, MESL, RSS, ERF–1 and ERF–2 showed no statistical difference between the values for paranoid type and the non-paranoid type at the initial or repeat test. Due to the small number of subjects in each subtype, it was statistically impossible to compare results between all subtypes.

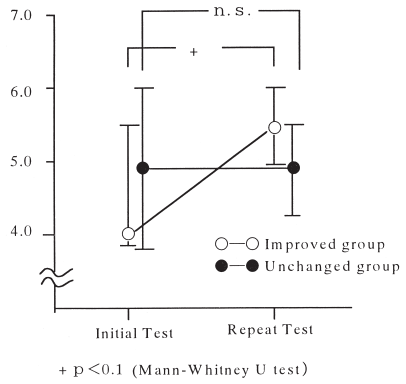

Fig. 4 Comparison of evaluation of reproduced figure-1 in 15 improved subjects and 13 unchanged subjects between the initial test and repeat test. Circles and bars show median ± quarters. A tendency ($p < 0.1$) was observed between the initial and repeat test in the improved group.

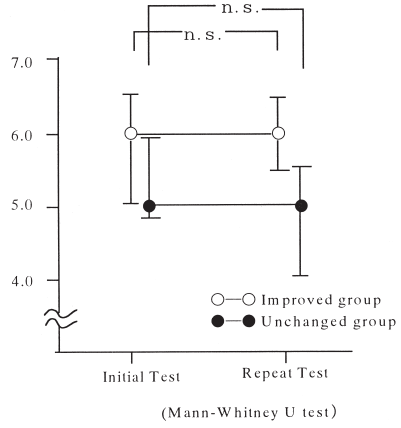

Fig. 5 Comparison of evaluation of reproduced figure-2 in 15 improved subjects and 13 unchanged subjects between the initial test and repeat test. Circles and bars show median ± quarters. No significant change was observed between the tests in either group.

Influence of neuroleptic drugs on exploratory eye movements

After the initial test, we compared the five indices of exploratory eye movements for eight patients that had never taken neuroleptic drugs (drug-naive group) with the 20 patients who were regular users (medicated group). No significant difference was found between the two groups, with the exception of the second drawing: NEF drug-naive 34.5 ± 6.9 vs. medicated 32.9 ± 5.8, n. s.; MESL 18.4 ± 3.9 vs. 16.6 ± 3.0, n. s.; RSS 9.3 ± 1.8 vs. 8.5 ± 1.3, n. s.; ERF–1 5.1 ± 1.1 vs. 4.4 ± 1.5, n. s.; ERF–2 6.2 ± 0.8 vs. 5.2 ± 1.0, $p < 0.05$. In addition, initial and retest results did not differ significantly between subjects in the drug-naive group.

Discussion

The results obtained in the present study, comparing the eye movements of schizophrenic and healthy subjects,

are consistent with those of previously published studies (Moriya 1972; Kojima et al. 1986, 1990, 1992). These results show that schizophrenic patients focus on a smaller number of eye fixation points and have a narrower range of eye movements on the memory task than healthy controls. Furthermore, the recorded number and range of responsive eye movements are limited during the comparison task and drawings from memory are less skilled for schizophrenic patients.

The aim of the current study was to investigate the relationship between exploratory eye movements and clinical symptoms in schizophrenic patients in repeat test design. Our hypotheses was as follows: Their eye movements would be more limited at the repeat test if their psychiatric conditions do not ameliorate. It is interesting to see changes of eye movements between the two tests if their psychiatric conditions ameliorate. A previous cross-sectional study showed there was no significant difference of eye movements variables between acute schizophrenics and remitted schizophrenics (Kojima et al., 1990).

First, it was necessary to ascertain the ways in which eye movements of normal controls changed using a series of the same tests over a period of more than 6 months. The results for the five test indices in the normal control group did not differ significantly between the initial and repeat test when tests were separated by a period of six months or more. This suggests that the test results can be reproduced, and that, no learning effect is apparent. Following normal control group testing, schizophrenic subjects were also tested twice, with a minimum six-month interval between tests. We observed that eye movements of patients were fewer and more limited in range at the times when they displayed the most severe symptoms. Furthermore, even in the group of patients who showed improved symptoms, the action of exploratory eye movement patterns did not significantly change. Paradoxically, some of the results of eye movement indices for schizophrenic patients worsened statistically in spite of improvement in their psychiatric conditions.

Although the symptoms of the schizophrenic patients improved as a group, the group included subjects whose symptoms improved and those whose did not. Therefore, in order to examine the relationship between the changes in exploratory eye movements and changes in symptoms, the schizophrenic patients were classified into an improved group and an unchanged group. No significant change in any of the 5 indices of eye movements of the 15 patients whose mental symptoms improved was detected between the initial and repeat test. Moriya (1979) showed that the healthy biological parents of schizophrenic patients displayed fewer exploratory eye movements that were more limited in range than those of healthy controls an the memory task test. This suggests that limited exploratory eye movements may be influenced by vulnerability to schizophrenia, rather than being a condition of a certain mental state. Xia et al. (1996) have also showed that healthy parents of schizophrenic patients demonstrate more limited responsive eye movements on the comparison task than healthy age-matched controls. These results suggest that limited frequency and range of responsive eye movement is strongly influenced by vulnerability to schizophrenia. Streit et al. (1997) conducted a psychophysiological study of the course of schizophrenia by examining the eye movements of schizophrenic patients shown an image of a human face in two tests conducted four weeks apart. In the first test they found a shorter length of mean scan path and a longer mean duration of fixation when compared to healthy subjects. These results did not change following the interim four-week period during which time the patients received treatment. The authors concluded that limited exploratory eye movements were not affected by treatment and were indicative of a schizophrenic trait.

On the other hand, change in eye movements was observed in subjects in the group whose symptoms remained unchanged. MESL value decreased significantly. This unchanged group, whose BPRS score remained unchanged over an approximate 8-month period, was regarded as the "model" of chronicity, because this group showed no improvement during various therapies, including neuroleptic medication, and negative symptoms persisted. Research conducted by Kojima et al. (1990) demonstrated that only the chronic patients group had significantly shorter MESL values than those of the normal control group. Neither the acute group nor the remitted group demonstrated scores significantly different from the control group, suggesting that shorter MESL values are linked to a chronic process of schizophrenic. The present study found that patients in the unchanged group who displayed psychopathological symptoms, especially negative ones, had significantly shorter MESL values, which also supports the hypothesis.

Patients as a whole group had a tendency for lower RSS values in the repeat test, indicating that this index is also influenced by the development of chronicity. Matsushima et al.(1998) have suggested that low RSS values are specific to schizophrenia and RSS is the most valid eye movement index for discriminating schizophrenia from other psychiatric conditions. Negative correlations in the chronic group have also been reported between RSS and emotional withdrawal and between RSS and blunted affect (Kojima et al., 1992). A significant decrease in RSS and NEF values has been previously reported between chronic and remitted groups of patients. Subjects in the chronic group received lower scores (Kojima et al., 1990). In the present study, we could not show that the unchanged group had lower RSS or NEF values approximately 8 months apart, which may be due to small sample size of the group.

Being different from RSS, low NEF values are shown in not only schizophrenics but a variety of psychiatric patients including depressed patients (Kojima et al., 1992). Interestingly, they also showed low NEF values of depressive patients improve according to the improve-

ment of the depressive condition. However, the present study showed low NEF values remained although BPRS scores were improved. Moriya (1979) showed low NEF values in schizophrenics' healthy parents. These results may be the reasons why NEF is the second valid eye movement index for discriminating schizophrenia from other psychiatric conditions.

We believe that different subtypes may display characteristic eye movements, but the results of the present study showed no difference between paranoid type and non-paranoid type subjects upon initial and repeat testing. We believe this issue should be addressed in further research. In Nakamura's study (1997), 120 schizophrenic patients were divided by subtype according to DSM-III-R criteria, and the relationship between various exploratory eye movement measurements and subtypes were examined. Results showed that disorganized-type patients had a significant decrease in the RSS compared to all other subjects. However, other measurements did not differ significantly among the subtypes, indicating that schizophrenia is characterized by distinctive eye movements regardless of subtype. The change over time in exploratory eye movements cannot be explained fully in terms of subtypes. It can be said that eye movements reflect aspects other than the clinical expressions which are important for classifying subtypes.

The present study also attempted to detect the unavoidable influence of medication in such long-term clinical investigations. The effects of neuroleptic drugs on exploratory eye movements have been the subject of past studies by Moriya (1979) and Kojima et al. (1990, 1992). These three studies found no significant correlation between eye movement and dosage in 80, 50 and 25 chronic schizophrenic patients when studying the relationship between eye movements and daily doses of chlorpromazine equivalents. In addition, Kojima et al. (1989) reported that the exploratory eye movements of 10 American schizophrenic patients did not differ significantly prior to and after medication. However, some patients had been classified as "unmedicated" although they had taken neuroleptics at some time in the past. Therefore, in the present study we compared the eye movements of eight unmedicated schizophrenic patients (drug-naive group) with those of 20 medicated patients (medicated group). Results showed that NEF and RSS did not differ significantly between the two (medicated and drug-naive) groups. Given these results, we conclude that neuroleptic medication has no effect on the exploratory eye movements in the tests conducted. Therefore, neuroleptic medication appears unlikely to strongly influence eye movements examined.

As explained above, the group of improved patients exhibited no change in eye movement patterns at the initial and repeat test of eye movement function, whereas the group of patients whose condition had not improved exhibited decreased eye movement value. We conclude that both trait and mental state affected this result. Few other psychophysiological studies have reported changes in indicators specific to schizophrenia over time. We believe that further research is necessary to compare exploratory eye movements in a greater numbers of subjects presenting with a variety of symptoms.

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