SHORT COMMUNICATIONS

Screening of Genetic Risk among Relatives and the General Public: Exploring the Spectrum of the Psychosis Prodrome

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ABSTRACT

Objective: **A large percentage of subjects with self-reported psychotic-like experiences (PLE) are found in the community and their status is unclear. The aim of the study is to detect the prevalence of non-affective psychosis and those with PLE among the relatives of patients with schizophrenia and the general public.**

Materials and methods: **This was a two-stage procedure involving the first and second degree relatives of patients with schizophrenia and the general public. In the initial stage, the subjects were screened using a Screening Questionnaire (SQ). The positive subjects proceeded to the second stage and were assessed using the Comprehensive Assessment of At-Risk Mental State (CAARMS), the Global Assessment of Function (GAF), Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HARS).**

Results: **A total of 660 subjects equally divided between the two groups formed a final sample. In the first stage, 170 (26%) subjects had positive scores on the SQ which was significantly higher in the general public. In the second stage, 34 (20%) cases were found to be positive, with a higher proportion among the relatives at genetic risk. The numbers of subjects with sub-threshold of attenuated psychotic symptoms (STAPS) (27%) and STAPS with affective symptoms (STAPSAS) (32%) detected was higher than those at Ultra High Risk (UHR) (23%) and non-affective psychosis (18%). Although no significant difference in the number of specific cases was detected between the general public and relatives at genetic risk, the proportion of relatives at genetic risk steadily increased as the illness progressed to full blown psychosis.**

Conclusions: **Clinical assessment or re-interview following a self-report questionnaire is mandatory to detect individuals with psychotic disorders. The prevalence of subjects with elementary PLE (sub-threshold of APS) was higher than subjects with established psychotic symptoms such as UHR individuals. The prevalence of depression was high in pre-psychotic states before the psychotic symptoms became prominence. The contribution of genetic factors was more prominent as the illness progresses to frank psychosis.**

KEY WORDS

attenuated psychosis, early psychosis, psychotic-like experiences, psychosis prodrome, self-report questionnaires

INTRODUCTION

The benefits of early intervention in schizophrenic psychosis have been well-documented[1]. Compelling evidence suggests that a shorter duration of untreated psychosis (DUP) is associated with a more favorable illness outcome with regards to symptomatology, hospitalization and remission rates, relapse, social and cognitive functioning, and response to medication and courses of treatment[2,3]. Identification of individuals at high risk of developing a psychotic disorder is therefore a compelling research goal. This would then potentially prevent full-blown psychosis, minimizing symptoms or disability and hence improving outcomes[4]. The 'at-risk'[5] period—which is sometimes called prodromal[6], ultra high risk (UHR)[7] or clinical high risk (CHR)[8]—is defined by worsening positive and negative symptoms, and a deteriorating course of psychosocial impairment culminating in the onset of frank psychosis.

Despite the growing optimism about prevention, little is understood about the basic characteristics of the prodrome or about its developmental course. There is a lack of solid, prospective data available to indicate the extent to which prodromal risk factors actually predict schizophrenia[3,9]. Although prevention in this case will be secondary, the search for prodromal risk factors is currently considered 'cutting edge' from a risk research prospective[10]. Genetic high-risk studies have indicated that subtle deficits can be identified long before psychosis emerges and that these deficits can serve as predictors of later schizophrenia. The premorbid phase of schizophrenia is characterized by social and cognitive deficit; alongside subtle neurological abnormalities which long precede the first episode of psychosis[11].

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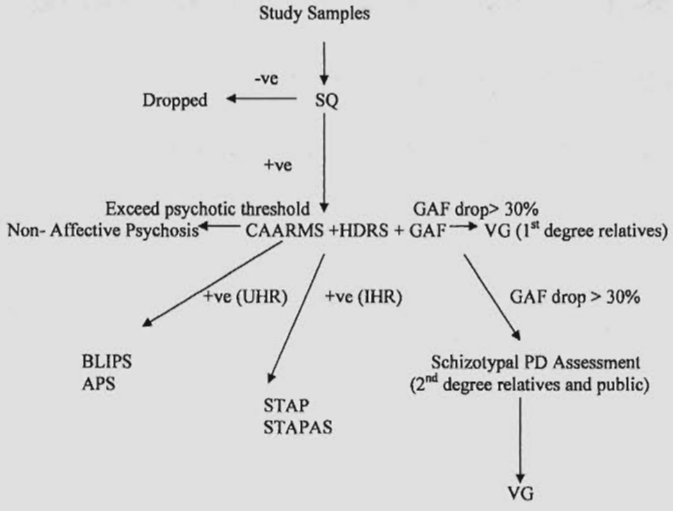

Figure 1. Flow chart of the screening

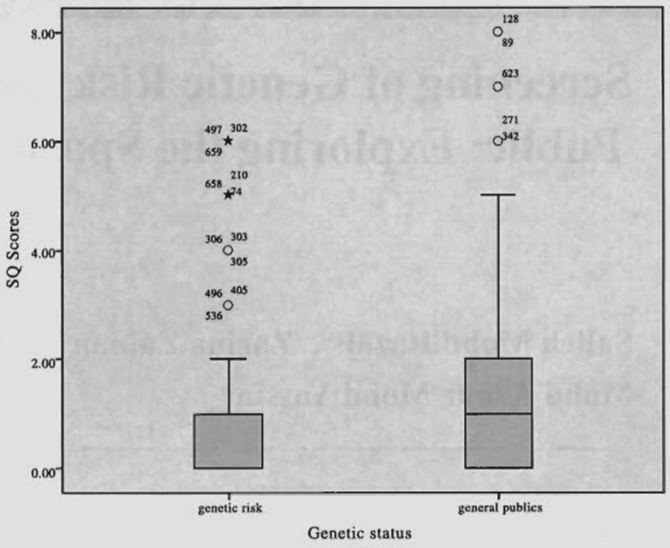

Figure 2. The SQ scores of relatives at genetic risk vs. general public

A few studies[12-14] have reported that the majority of self-reported psychotic-like experiences (PLE) have not been found to be associated with a psychotic disorder and will disappear over time. A systemic review and meta-analysis found that the yearly conversion rate to a clinical psychotic outcome in individual with sub-threshold psychotic experiences was 3.5 times higher than for individuals without experiences and there was the evidence of dose-response with severity/persistence of psychotic experiences[15]. The onset of psychosis typically emerges in young people, with 80% of first episodes occurring between ages 16 to 30 years[16]. Current research found that individuals at risk of psychosis demonstrate early anxiety and mood disturbances, especially depression in addition to prominent functional disability[4,17,18]; even depression and anxiety are often the first symptoms to emerge in psychosis[17]. Yung *et al*[18] pointed that affective disturbance such as depressive symptoms are frequently marked the onset of the initial prodrome of psychosis. Depression has also been found to be an important factor in mediating outcome in those with PLE in the community and UHR populations[19].

We implemented a two-stage procedure to detect individuals with non-affective psychosis and at risk for psychosis among the relatives of Malay patients with schizophrenia and compared them with the general population. The specific objectives of this study were to detect subjects at UHR and sub-threshold of Attenuated Psychotic Symptoms (APS); and explored the associated affective symptoms, especially depression and anxiety which are common in early psychosis[4,17-19]

MATERIALS AND METHODS

Subjects

In this study the sample was divided into two groups of equal size. The first group consisted of the relatives of Malay patients with schizophrenia, while the second group was from the general population of ethnic Malays. More than 90% of the population in the location of the study, the north-eastern part of Peninsular Malaysia, is Malay. Another 8% are Chinese and Indian, forming the minority group. The sample was selected through convenience sampling. The first and second degree relatives of patients with schizophrenia (DSM-IV-TR)[20] from 12 to 30 years old were approached to take part in the study when they visited the psychiatric ward during visiting hours or accompanied psychiatric patients to the psychiatric clinic of Hospital USM for a follow-up visit. If they agreed to take part in the study, other family members were then contacted to arrange an interview. Some of the relatives were interviewed at home with the assistance of the Community Mental Health Team (CMHT). Members of the general public within the same age group without a family history of schizophrenia among their first and second degree relatives were also selected through the same sampling method. They were chosen from among the patients' neighbors during community visits, hospital visitors, pedestrians, job-seekers, general workers, and school and college students. The study protocol had been approved by The Ethical Committee (Human), Universiti Sains Malaysia (USM).

Exclusion criteria

Subjects were excluded if they:

a. declined to sign informed consent;
b. had been treated for psychotic illness or were being treated with antipsychotic drugs;
c. had co-morbid substance abuse, mental retardation, organic mental disorders or other related conditions.

Assessment

Initial Screening

The preliminary (first stage) screening was conducted by research assistants (RA). All the selected subjects were screened using a Screening Questionnaire (SQ). The SQ, which was modified from the SIPS screen[21], consisted of 10 items of positive symptoms requiring a dichotomous 'yes' or 'no' response. The SQ was translated into Malay and had been validated previously. The sensitivity and specificity of the SQ at the cut-off point of 2 was 77.5% and 93.5% respectively[22]. Those subjects who scored 2 and above would proceed to the second stage.

Second Stage Screening

The second stage assessment was conducted by the research psychiatrists using the Comprehensive Assessment of At-Risk Mental State (CAARMS)[23]. The Hamilton Depression Rating Scale (HDRS)[24] and Hamilton Anxiety Rating Scale (HARS)[24] were administered to evaluate the severity of depression and anxiety respectively. The screening process and assessment are summarized in a flow chart (Figure 1). The overall level of function was assessed using the DSM-IV-TR Global Assessment of Function (GAF) scale[20]. If positive symptoms were detected (disorders of thought content, perceptual abnormalities and disorganized speech), further exploration was required to assess the severity, frequency and duration of symptoms. Further assessment was conducted with the schizotypal personality disorder (PD) check list[20] for second degree relatives and the general public.

The positive subjects were classified according to 5 main categories:

(i) Full-blown non-affective psychosis (schizophreniform disor-

der/schizophrenia) if the subjects reached or exceeded the psychotic threshold as defined in CAARMS[23]

Two of the three operationally defined UHR sub-groups[23] were categorized as:

(ii) Brief limited intermittent psychotic symptoms (BLIPS) or attenuated psychotic symptoms (APS).

The primary degree relatives and other subjects with schizotypal PD who had least 30% drop in GAF score from premorbid level, sustained for a month were classified as the third subgroup of UHR[23]

(iii) Vulnerable group (VG).

We created another category (sub-threshold of APS) for lower risk subjects in which the positive symptoms were less severe (sub-threshold intensity) or present in low frequency (sub-threshold frequency), but fulfilled other criteria of APS; such as the symptoms present in past year and for not longer than 5 years as defined in CAARMS[23].

(iv) Sub-threshold of APS (STAPS).

The operational criteria of STAPS are as follows:

Sub-threshold intensity: Severity scale score of 2 on disorder of thought content subscale, 2 on perceptual abnormalities subscale and/or 3 on disorganized speech subscales of the CAARMS[23] Plus

: Frequency scale score of 3-6 on the disorder of thought content, perceptual abnormalities and/or disorganized speech subscales of the CAARMS[23] for at least a week or frequency scale score of 2 on disorders of thought content, perceptual abnormalities and disorganized speech subscales of the CAARMS[23] on more than 2 occasions

Sub-threshold frequency: Severity of scale score of 6 on disorder of thought content subscale, 5- 6 on perceptual abnormalities subscale and/or 6 on disorganized speech subscales of the CAARMS[23] Plus

: Frequency scale score of 2 on the disorder of thought content, perceptual abnormalities and/or disorganized speech subscales of the CAARMS[23]

Subjects with STAPS in addition to positive HDRS[24] scores and/or HARS[24] scores, they were classified separately as:

(v) STAPS with affective symptoms (STAPSAS).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., IL., USA). The Mann-Whitney U-test was used to assess continuous data and categorical data were analyzed using the chi-square test since the data were non-parametric. Results were considered statistically significant at $p < 0.05$.

RESULTS

Initial screening

Finally, 660 subjects, equally divided between the two groups, entered the initial screening. Out of 330 relatives at genetic risk, 239 (72.4 %) were first degree relatives, while 91 (27.6 %) were second degree relatives. The mean age of the relatives at genetic risk was 19.35 (SD 5.2) years, while for the general public the mean age was 21.31 (SD 3.9) years. There were no significant differences in age, sex and highest educational status between the subjects in both groups. There were 170 subjects (25.8%) from both groups who had positive scores on the SQ (scored 2 and above) and proceeded to the second stage of screening. Of these, 110 were from the general public and 60 were relatives at genetic risk.

The SQ scores and socio-demographic variables

The mean SQ scores for both groups was 1.015 (SD 1.49). The mean SQ scores for the general public and relatives at genetic risk were 1.285 (SD 1.63) and 0.746 (SD 1.27) respectively. The mean score for the general public was significantly higher than that for relatives at genetic risk ($Z = -4.721$, $p < 0.001$). The distributions of the SQ scores for both groups are displayed in Figure 2. There were no significant differences in age, gender and highest level of education between those who scored positively and negatively on the SQ. However, the numbers of the general public who scored positively on the SQ (33.3%) were significantly higher than the relatives at genetic risk (18.2%) ($\chi^2 = 19.808$, $df = 1$, $p < 0.001$) (Table 1).

Second stage screening

Out of 170 subjects who proceeded to the second stage, 34 (20%) were found to be positive. The distribution of the detected cases is shown in Table 2. The overall prevalence of STAPS and STAPSAS (3%) was higher than Ultra High Risk (UHR) (1.2%) and non-affective psychosis (0.91%). Twenty (59%) subjects had elementary PLE (9 STAPS and 11 STAPSAS) as compared to 8 subjects at UHR (23%) and 6 cases of schizophrenia/schizophreniform disorder (18%). Among 8 subjects at UHR, 7 were APS and only1 BLIPS. No cases of VG were detected. A few cases of major depression without psychosis and 2 cases of major depression with psychosis were detected, but they were excluded from the study. In the second stage, 21 subjects detected were relatives at genetic risk; the number of detected cases was significantly higher among relatives at genetic risk (35%) as compared with the general public (11.8%) ($\chi^2 = 13.040$, $df = 1$, $p < 0.001$). Although no significant difference in the number of specific cases was detected between the general public and relatives at genetic risk, the prevalence of relatives at genetic risk steadily increased as the illness progressed to frank psychosis.

DISCUSSION

The results show a remarkable difference between the SQ scores and clinical assessment in the second stage. However, after the interview in the second stage, the number of true positive cases dropped drastically in both groups. Approximately 33.3% of the subjects from the general public and 18.2% of the relatives at genetic risk had psychotic symptoms based on the SQ scores; this dropped to 3.9% and 6.4% respectively after the interview was conducted using CAARMS[23]. The drop in the number of positive cases was higher among the general public (29.4%) as compared with relatives at genetic risk (11.8%). The study also found a significant difference between the SQ scores for the general public and those for relatives at genetic risk. However, the scores were not influenced by the age, gender and educational status of the subjects. One explanation for the difference is that at-risk subjects without a psychotic-level conviction of their experiences rather overestimate their symptoms in the same way as people in the general population. In contrast, psychotic or schizophrenia patients may underestimate their experiences because of the unrealistic natures of their experiences, beliefs, and so on[25,26].

A few other studies have reported a similar discrepancy between self-reported PLE and the prevalence of psychosis, although difference methodology was used. In other words, prevalence figures for self-reported PLE are high, while the frequency of individuals fulfilling the criteria for schizophrenia or non-affective psychosis is low. Ochoa *et al*[27] found that 11.8% of the general population reported psychotic symptoms, but the prevalence of psychotic disorders was between 0.85 to 2.37%. In The National Comorbidity Study, Kendler[28] found that 28.4% were screened positive for any type of psychotic experience; whereas the prevalence of broadly defined psychosis was only 0.7%. Recently Grano *et al*[29] found a significant difference between psychosis risk scores based on self-report versus interviews with adolescents.

We found that the prevalence of detected cases was higher among the relatives at genetic risk (63.6%) than in the general population (39.4%). The overall prevalence was higher in STAPS and STAPSAS (3%) as compared with UHR (1.2%) and non-affective psychosis (0.91%). The strong link to genetic factors is also supported by the finding that the proportion of relatives at genetic risk increased as the illness progressed to full-blown psychosis; i.e. from 60% (STAPS/ STAPSAS) to 62.5% (UHR), and to 62.5% and 66.7% (schizophrenia/schizophreni-

Table 1. The relationship between positive SQ scores with age, gender, genetic status and educational status

Variables	Positive SQ n = 170 (n%)	χ^2 (df) / Z	p - value
1. Age (year)		-0.167	0.867*
Mean (SD)			
Female	20.08 (5.21)		
Male	20.46 (4.45)		
2. Gender		2.678 (1)	0.102
Female	48 (21.8)		
Male	122 (27.7)		
3. Genetic Status		19.808 (1)	< 0.001
Public	110 (33.3)		
Genetic risk	60 (18.2)		
4. Educatinal Status		4.004 (5)	0.549
Primary School	7 (20)		
Lower Secondary	26 (22.4)		
Upper Secondary	66 (27.5)		
College / Diploma	58 (28.7)		
University	12 (19.4)		
Professional degree	1 (3)		

*Mann-Whitney Test

Table 2. The distribution of detected cases in the second stage of screening

Diagnoses	Relatives at genetic risk (n = 21)	General public (n = 13)	Total (n%) (n = 34)
1. Schizophrenia/ Schizophreniform disorders	4	2	6 (18)
2. BLIPS/APS	5	3	8 (23)
3. STARS	5	4	9 (27)
4. STAPSAS	7	4	11 (32)

form disorders). The prevalence of schizophrenia/schizophreniform disorders among relatives at genetic risk was 1.2%, which is much lower than expected. About 8% of siblings and 12% of children of schizophrenic individuals will develop schizophrenia compared to approximately 1% in the general population[30]. The lower result found in this study is probably due to the weakness in sampling and narrow age range of the study population (12-30 years old). The prevalence of subjects with PLE or sub-clinical psychosis (STAPS, STAPSAS and UHR) was 4.2%; it was lower than the median prevalence of about 7% as reported in the previous meta-analysis from the cohort study[31] and among adolescents aged 13 to 18 years[32]. The lower prevalence found in this study is partly due to the differences in screening procedure and population sampling, and low sensitivity of the screening questionnaires (SQ).

The prevalence of STAPSAS (1.7%) was slightly higher than STAPS (1.4%) or 55% of the subjects with sub-threshold of APS had associated depression and/or anxiety. This showed that depression was common in the pre-psychotic states, such as in sub-threshold of APS before the psychotic symptoms was well-established. Depression has been found to be a significant predictor of psychosis in the UHR groups[18] and an important factor in mediating outcome in those with PLE in both community and UHR populations[19]. It also associated with increased risk of transition to psychotic disorder in the UHR group. Yung *et al*[19] also stressed the importance of assessment of depression in those with PLE and consider the need for treatment of the co-morbid depressive syndrome, which may reduce the risk of worsening of PLE and transition to psychotic disorder.

One hundred and seventy (26%) of the sample screened positive on the SQ, but only 14 (8.2%) of them were positive (full blown psychosis and UHR) in the second stage. This shows that the sensitivity of the SQ was lower than 77.5% as found in the previous validation study[22]. It is hard to explain but probably the study subjects tend to minimize or hidden their symptoms because they knew that they were being screened for mental illness. In Asian culture, the stigma towards people with severe mental illness (SMI) was strong; the public tend looks down on them and their families[33]. Other possibilities that the subjects did not really understand or interpret differently the self-report questionnaires (SQ); especially majority of them were in the young age and could not differentiate between psychotic symptoms and normal experiences. Thus, this study support the need of clinical assessment or re-interview following a self-report questionnaire in detecting individuals with psychotic disorders among the general population.

There are pro and con regarding screening of psychosis in the general population. The aim of the screening is to start early intervention so that those detected (at-risk subjects) do not progress to full blown psychosis. In a systemic review and meta-analysis, Van Os *et al*[34] found that approximately 75-90% of subjects with subclinical or sub-threshold PLE is transitory and disappeared over time. Thus, the subjects such as STAPS and STAPSAS do not require treatment in view of low conversion risk. The controversies arise for subjects at UHR; especially with the recent finding that the transition rate to psychosis had declined to 19% at the 18 months follow-up[35] and to 16% at the two years follow-up[7], which are unfavorable for pharmacological intervention. A recent study[36], which found that majority of the at-risk subjects who did not transition to full-blown psychosis over 2 years were improved with fewer symptoms and better functioning, indicating that antipsychotics treatment generally is also not required. This is in accordance with de Koning *et al*[37] conclusion in their review that at present, the data concerning the benefits and risks do not justify prodromal intervention as a standard clinical practice.

This supported by the finding that the prodromal symptoms are non-specific[3,18] and we are not sure which individuals would benefit from antipsychotic treatments; otherwise they were unnecessarily treated with antipsychotics and might develop side-effects, as well as being labeled as mentally ill. There are also suggestions that contrary to expectation the antipsychotic drugs may not be able to prevent the transfer to psychosis[38]. The treatment with antipsychotics drugs may be palliative and just delay the onset of psychotic disorders; the rate of conversion and exacerbation of prodromal symptoms is increased after discontinuing antipsychotic treatment[39]. The finding that the transition to psychosis is at greater risk if the subjects are help-seeking who meet UHR or prodromal criteria is another setback for public screening[7,36]. However, a small group of individual at-risk who deteriorated rapidly, dangerous to the others, had aggressive behavior and severe suicidal risk is indicated for antipsychotic treatment[40]. Those detected with schizophreniform disorder/schizophrenia were most benefited from the screening program because early antipsychotic treatment will shorten the DUP and improved prognosis[2,3].

Nevertheless, the present study also has several limitations, such as a small sample size, the use of convenience sampling (selecting subjects who happened to be available), and the fact that the two study groups were not matched. These methodological weaknesses would exclude some positive cases and result in low prevalence. Universal sampling is better for a prevalence study and the important parameters such as age, gender and educational status between the two groups should be controlled in order to get a homogeneous sample.

CONCLUSION

Clinical assessment or re-interview following a self-report questionnaire is mandatory to detect individuals with psychotic disorders in general population. The prevalence of depression was high in pre-psychotic states, such as in sub-threshold of APS before the psychotic symptoms was prominence. The status of individuals with sub-threshold of APS remains uncertain and needs further study; especially the prognostic differences between those with affective symptoms (STAPSAS) and without affective symptoms (STAPS). It would be interesting to followed-up them in the long term and assess the rate of transition to UHR and psychotic disorders. The prevalence of subjects with elementary PLE such as STAPS and STAPAS was higher than subjects with established psychotic symptoms such as UHR individuals. The contribution of genetic factors cannot be taken lightly since the proportion of relatives at genetic risk increased steadily as the illness progressed to full-blown psychosis.

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