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Screening for schizophrenia in initial prodromal phase: Detecting the sub-threshold psychosis

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ABSTRACT

Objectives: The aim of the study is to screen and evaluate the efficacy of the screening tools in detecting subjects with sub-threshold psychosis among asymptomatic individuals at genetic risk, as compared with persons in the general public.
Methods: This was a two-stage study of the relatives of patients with schizophrenia and general individuals. Subjects were screened with a Screening Questionnaire (SQ) and General Health Questionnaires (GHQ-12) in the initial stage. Those who screened positive were reassessed using the Comprehensive Assessment of At-Risk Mental State (CAARMS) in the second stage.
Results: A total of 190 (29%) subjects initially screened positive from a sample of 660 individuals. The proportion of persons in the general public (63%) who progressed to the second stage was significantly higher than at-risk relatives (37.4%) ($X^2 = 17.028$, $df = 1$, $p < 0.001$). After final assessment, about 4% of the sample was positive; subjects at sub-threshold UHR (ultra-high risk) was higher (69%) than subjects at UHR (31%). Detection rate was higher when both GHQ and SQ (26.4%) measures were positive in the initial screening. In both categories of sub-threshold psychosis, the percentage of subjects at genetic risk was higher (62%), and the proportion steadily increased as the psychosis progressed.
Conclusion: The prevalence of sub-threshold psychosis was higher in subjects at genetic risk. Clinical assessment following a self-report questionnaire should be mandatory as the rate of false positive results is high. The SQ has poor validation indexes, which is partly contributed to low detection rate and the GHQ is not suitable for screening early psychosis.

1. Introduction

It is believed that individuals who will develop schizophrenia go through a variety of abnormal subjective experiences that progressively develop during pre-puberty and puberty. Genetic high-risk studies have indicated that subtle deficits can be identified long before psychosis emerges and these deficits can serve as predictors for later development of schizophrenia. Ideally, the prevention should be conducted during these years to detect the disease before symptoms are evident and progress to psychosis. The participants in most of the studies were help-seeking adolescents who were already affected by psychotic-like symptom. Such people cannot be targeted with primary prevention because it is highly probable that an actual disease process has already begun (Cornblatt et al., 2002). The intervention should be aimed at high risk individuals showing minimal but detectable signs of possible incipient mental disorder, and who do not meet the current diagnostic criteria.

There are a number of variables that confer some indication of vulnerability to schizophrenia. Screening instruments have been developed that incorporates vulnerable factors. However, there is no single instrument capable of detecting individuals in the prodromal phase with satisfying degrees of sensitivity and specificity (Kline et al., 2012). Basic Symptoms (BSs) which is presumably characterise the early prodromal phase, are closely linked to hypothetical core vulnerability of schizophrenia. These disturbances are presumed to be the phenotype of underlying neurophysiological deficits. The BSs are experiential, not behavioural in kind and only recognisable by the self-report of the patients. BSs are subjectively experienced disturbances of perception, cognition, language, motor function, will, initiative, level of energy and stress tolerance (Gross, 1997), operationalized by the

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Bonn Scale for Assessment of Basic Symptoms (BSABS, Gross et al., 1987), or the shorter version, Schizophrenia Prediction Instrument-Adult Version (SPI-A, Schultze-Lutter et al., 2004). The BSABS operationalization of prodromal symptoms performed well in the early detection of schizophrenia (Klosterkotter et al., 2001).

The ability to identify asymptomatic individuals at high risk for psychosis through low cost screening is greatly beneficial. The screening instrument is used in the first phase of a two-stage study, which is followed by assessment either with the Comprehensive Assessment of At-Risk Mental State (CAARMS, Yung et al., 2002) or the Structured Interview for Prodromal Symptoms (SIPS, McGlashen et al., 2003) in the second stage. The CAARMS and SIPS as well as the other commonly used screening instruments such as Prodromal Screening (PROD-Screen, Heinima et al., 2003), Prodromal Questionnaires (PQ, Loewy et al., 2005) and SIPS Screen (Miller et al., 2004) are based on the attenuated positive syndrome (APS) approach, which is aimed to detect the late prodromal phase, but less useful for detecting early psychosis (Olsen and Rosenbaum, 2006). While the BSABS (Gross et al., 1987) is more sensitive in detecting early prodromal phase.

Screening instrument with good validation indexes should be able to assess correctly asymptomatic individuals at risk (Corcoran et al., 2005). The objective of the study is to detect subjects at sub-threshold psychosis among the relatives of patients with schizophrenia and people of the general public; and evaluate the efficacy of the screening tools. There is a growing consensus in the field that UHR and BSs approach are complementary, providing criteria to detect different prodromal stages (Phillips et al., 2005). In contrast, this study is exploring the utility of a single screening instrument in detecting subjects at the earlier (sub-threshold UHR) and late prodromal stage (UHR). We would use a previous local screening questionnaire (Razali et al., 2011), which is design mainly to cover APS psychopathology, and the General Health Questionnaires (GHQ-12) in the initial stage. We hope to evaluate the sensitivity of APS psychopathology and usefulness of GHQ-12 in screening early psychosis.

2. Methods

2.1. Subjects

The selected subjects were divided equally into two groups, which were chosen through convenience sampling. The first and second degree relatives of patients with schizophrenia (DSM-IV-TR, American Psychiatric Association, 2000) between 12 and 30 years formed the first group; while the second group consisted of individuals from the general population within the same age group. The relatives of patients was selected for the study when they visited psychiatric ward during visiting hours or when they accompanied psychiatric patients to the psychiatric clinic of Hospital USM. Other members of the family were then contacted through telephone to arrange for an interview at home with the assistance of the Community Mental Health Team (CMHT) if they agreed for the study. Members of the general public were chosen from among the patients' neighbours, house-wives, hospital visitors, pedestrians, civil servants, hospital administrative staff, schools and college students. The Ethical Committee (Human), Universiti Sains Malaysia (USM) reviewed the research protocol and then approved the study.

2.1.1. Exclusion criteria

Subjects in both groups were excluded if they:

(i) declined to sign informed consent, or
(ii) had past history of psychotic illness or being treated with neuroleptics, or
(iii) had co-morbid substance abuse, mental retardation or organic mental disorders

Individuals from the general population were excluded if they:

(i) had history of major psychotic illness among the first and/or second degree relatives.

2.2. Assessment

2.2.1. Initial screening

Research assistance (RA) started the preliminary (first stage) screening using a validated Malay version of Screening Questionnaire (SQ) (Table 1) and the General Health Questionnaires (GHQ-12). The SQ is a 10-item question mainly covering APS psychopathology, which was modified from the SIPS (McGlashen et al., 2003). The cut-off scores of the SQ and GHQ-12 was 2 and 3 respectively (Razali et al., 2011).

2.2.2. Second stage screening

The research psychiatrists conducted the second stage assessment using the Comprehensive Assessment of At-Risk Mental State (CAARMS) and two other research tools, as summarized in the flow chart (Fig. 1). If positive findings were detected from CAARMS, they were further explored to assess the severity, frequency and duration of the symptoms. The Global Assessment of Function (GAF) scale (DSM-IV-TR, American Psychiatric Association, 2000) was then used to evaluate the current level of function. The presence of schizotypal personality disorder (PD) in second degree relatives and general individuals when their GAF scores dropped more than 30% from premorbid level was assessed with The Structured Clinical Interview for DSM-IV (SCID, American Psychiatric Association, 1994).

The positive subjects were classified according to two main categories: UHR (early prodromal stage) and sub-threshold UHR (late prodromal stage)

(i) The UHR category is further divided to two sub-groups (Yung et al., 2004a):
  (a) Brief limited intermittent psychotic symptoms (BLIPS) or attenuated psychotic symptoms (APS).
  (b) Vulnerable group (VG): The primary degree relatives and other subjects with schizotypal PD who sustained at least 30% drop in GAF score from premorbid level for a month.
(ii) A sub-threshold UHR category consists of sub-threshold APS (STAPS) and sub-threshold BLIPS (STBLIPS) in which the positive symptom (severity scale score) is less severe or the

Table 1
The Screening Questionnaires (SQ).

No.	Psychphatology assessed
1	Perceptual disturbances (auditory)
2	Suspiciousness/Persecutory idea
3	Perceptual disturbances (visual)
4	Unusual thought content
5	Impaired ability to initiate social contact
6	Delusional ideas
7	Delusion of being controlled/thought interference
8	Clairvoyance/Sixth sense
9	Conceptual disorganisation
10	Distorted body experiences/impaired bodily sensation

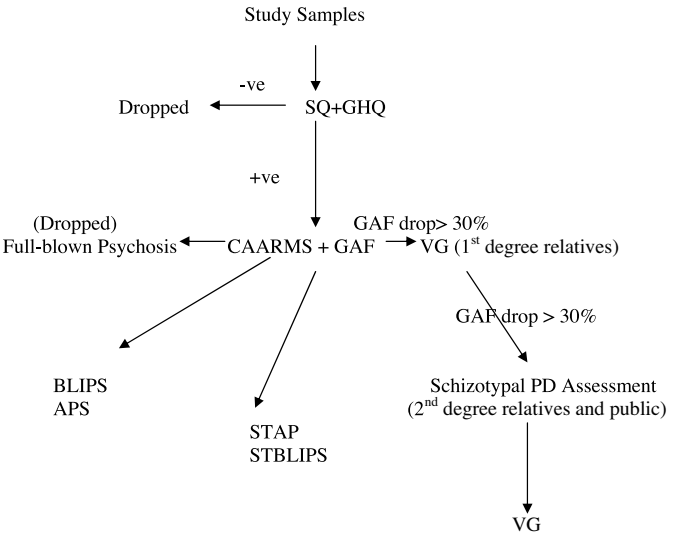

Fig. 1. Flow chart of the screening.

score is below the threshold of UHR, and fulfilled other criteria of APS or BLIPS.

The operational criteria of sub-threshold UHR was defined as below (Yung et al., 2004a):

(a) Sub-threshold of APS (STAPS): *Sub-threshold intensity*: Severity scale score of: 2 on disorder of thought content subscale, 2 on perceptual abnormalities subscale, 3 on disorganised speech subscales of the CAARMS, or a combination of these. *Sub-threshold frequency*: Severity scale score of: 5 on the disorder of thought content, 4 on perceptual abnormalities, 5 disorganised speech subscales of the CAARMS, or a combination of these.
(b) Sub-threshold of BLIPS (STBLIPS). Severity scale score of 5 on the disorder of thought content subscale, 4 on perceptual abnormalities subscale, 5 on disorganised speech subscale of the CAARMS, or a combination of these.

The subjects who scored higher than the psychotic threshold according to CAARMS or developed full blown non-affective psychosis (schizophrenia/schizophreniform disorder) were excluded from the study

2.3. Sample size and statistical analysis

We used single proportion formula to determine the sample size. Based on the median prevalence rate of 5% of sub-clinical psychosis in general population (Van Os et al., 2009) with 95% confidence interval and $Z = 1.96$, the calculated sample size is 73. Data were analysed using SPSS for Windows, version 16.0 (Chicago, IL., USA). Continuous data and categorical data were examined using the Mann–Whitney *U*-test and the chi-Squared test respectively. The statistical tests were two-tailed, with the level of significance set at $p < 0.05$.

3. Results

3.1. Initial screening

There were 330 subjects in each group. Majority (72.4%) of the at-risk relatives were first degree relatives and the mean age of this group was 19.35 ± 5.2 years; while the mean age of general individuals was 21.31 ± 3.9 years. The subjects in both groups had no significant differences in age, gender and highest level of education. A total of 190 (29%) subject initially screened positive and they proceed to the second stage of study; of these, 71 (37%) were at-risk relatives and 119 (63%) were individuals from the general public.

3.2. Second stage screening

3.2.1. Distribution of cases

In the second stage of assessment, a total of 35 subjects which comprised 22 at-risk relatives and 13 general individuals screened positive. However, 6 subjects were excluded because they had exceeded the psychotic threshold and were diagnosed with schizophrenic form disorder/schizophrenia. Those with exceeded psychotic score were four subjects at genetic risk and two general individuals. The distribution of the 29 individuals with sub-threshold psychosis by their genetic status is shown in Table 2. There were 161 (85%) subjects with false positive, 108 were general individuals and 53 genetic at-risk relatives.

3.2.2. Distribution of GHQ and SQ

Fifty three subjects had positive scores in both GHQ and SQ. Altogether, 170 subjects were positive on SQ alone, 110 (33.3%) general individuals and 60 (18.2%) at-risk relatives. The number of general individuals with positive SQ score was significantly higher than at-risk relatives ($X^2 = 19.8079$, d$f = 1$, $p < 0.001$). Regarding the GHQ score, of 73 subjects who scored positive, 40 (12.1%) were general individuals. There were no significant difference between general individuals and at-risk relatives who scored positive on GHQ ($X^2 = 0.7931$, d$f = 1$, $p = 0.3732$). The distribution of the GHQ and SQ scores according to genetic status, was summarised in Table 3

3.2.3. Socio-demographic determinants of progressing to the second stage

The number of general individuals (62.6%) who progressed to the second stage was significantly higher than at-risk relatives (37.4%) ($X^2 = 17.028$, d$f = 1$, $p < 0.001$). Other socio-demographic variables such as age, gender and highest level of education did not influence the progression to the second stage (Table 4).

3.2.4. The detection rate of the screening tools

Among 190 positive subjects in the initial screening, a majority 117 (62%) was detected through SQ alone, while 53 (28%) were detected by both GHQ and SQ; only 20 (10%) were detected by GHQ. However, after the second stage screening, 29 cases of sub-threshold psychosis were identified. The distribution of the cases were summarised in Table 5. The SQ alone and the combination of the SQ and GHQ detected the same number of cases (14 cases each), while GHQ alone detected only 1 positive case. The combination of the GHQ and SQ also detected all 6 psychotic cases which were excluded

Table 2
Number of cases who proceed to the second stage assessment and the outcome of the assessment.

Proceed to the second stage					
Proceed	Genetic risk	Public	Total	X^2 (df)	P
Yes	71	119	190		
No	259	211	470		
Total	330	330	660	17.028 (1)	<0.001
Distribution of the positive subjects by genetic status					
Outcome	Genetic risk	Public	Total		
Positive	18	11	29		
Negative	53	108	161		
Total	71	119	190		

Table 3
The distribution of GHQ and SQ scores of the general public and relatives at genetic risk.

Scores	GHQ		SQ	
	Gen (%)	Public (%)	Gen (%)	Public (%)
0	246	193	207	155
1	34	69	63	65
2	17	28	26	42
3	10	19	20	25
4	9	6	5	27
5	7	6	3	11
6	4	3	6	2
7	1	1	0	1
8	0	2	0	2
9	2	2	0	0
10	0	1	0	0
Total	**330**	**330**	**330**	**330**

from the study. The detection rate was higher when both the SQ and GHQ were positive (26.4%), than when subjects screened positive with SQ (12%) or GHQ alone (5%). Three genetic at-risk individuals from second degree relatives had significant drop in the GAF score and proceed with schizotypal PD assessment; however, they did not fulfil the criteria of Schizotypal P.D (SCID, 1994). Thus, VG was excluded.

3.2.5. Final diagnosis and genetic status

Finally 29 (4%) subjects from the initial screening of 660 high risk relatives and general population were positive. Among 29 individuals with sub-threshold psychosis (UHR and sub-threshold UHR), a majority 18 (62%) were among the genetic at-risk relatives. Regarding the distribution of positive subjects, 20 (69%) were STAPS/STBLIPS (12 at genetic risk, 8 general individuals) and 9 (31%) were APS/BLIPS (6 at genetic risk, 3 general individuals). None of the subjects with VG was detected. It was observed that the genetic at-risk relatives' proposition steadily increased as the psychosis progressed; 67% UHR individuals were detected as compared with 60% subjects with sub-threshold UHR.

4. Discussion

The study found that about 4% of the screened population was positive for sub-threshold psychosis. Since they were not clinically psychotic, sometimes they were categorised as having psychotic Experiences (PEs) or Psychotic-like experience (PLE). The reported prevalence of PEs found in this study is not much different from the previous studies. DeVyider et al. (2014) found that 3.4% of the 10, 541 respondents in the general population reported PLE in the last 12 months; while the latest data from analysis of 31, 261 respondents in the WHO World Mental Health Survey of 18 counties (McGrath et al., 2015) revealed that 5.8% of them reported at least one psychotic experience in their life time, with hallucinatory experience being the most common (5.2%) as compared with delusional experience (1.3%). The detection rate in this study would be higher if the sampling method could be improved; with convenience sampling those likely to be positive cases may avoid from the study for fear of stigma or being labelled as mentally ill. In Asian culture the stigma towards people with severe mental illness (SMI) is strong; the public tends to boycott or look down on them and their families (Ng, 1997).

A higher percentage of subjects (69%) at sub-threshold UHR (STAPS/STBLIPS) were detected, as compared with subjects (31%) at ultra-high risk (APS/BLIPS). Both categories are present in a higher proportion (62%) among individuals at genetic-risk, indicating that genetic factors play an important role in the pathogenesis of major psychoses. Although individuals with PEs are common in the general population, STAPS/STBLIPS and UHR are two different categories. The status of UHR is more established and has been widely studied. The people with UHR yielded a conversion rate to full-blown psychosis of 30-50% (Yung et al., 2003, 2004b), while the people with sub-threshold UHR most likely had symptoms weakly associated with psychotic disorder that will disappear over time (Van Os et al., 1999, 2009). It is interesting to know why some people recover while others may progress to full blown psychosis. Van Os et al. (2009) proposed psychosis proneness-persistence-impairment model to predict the future development of psychosis, which is based on environmental exposure interacting with genetic risks. The other explanation is the presence of BSs in the individuals' subject. It was found that about 50% of subjects with BSs in early prodromal phase progressed to psychotic disorder within 9.6 years of follow up (Klosterkotter et al., 2001).

Various screening instruments have been constructed with the aim of recruiting individuals for further assessment. The success of any screening program much depends on the validity and reliability of the screening questionnaires. Loewy et al. (2012) for instance found good predictive validity for later development of psychosis in a two-stage screening processes, combining PQ and SIPS; which is contributed by good validation index of the PQ. The SQ and GHQ in this study seemed to have low sensitivity because a high percentage of the subjects detected in the initial screening were found to be false positive, and we speculate that its specificity is better than the sensitivity. The low validation indexes of the SQ are also contributed to low detection rate. This is consistence with

Table 4
The relationship between subjects who proceed to the second stage with age, gender, genetic status and educational background.

Variables	Proceed $N = 190$ (%)	X^2 (df)/z	p-value
Age Mean (SD)	20.37 (4.4)	−0.325	0.745*
Gender	136 (71.6)	2.897 (1)	0.089
Male	54 (28.4)		
Female			
Genetic		17.028 (1)	<0.001
Public	119 (62.6)		
Genetic risk	71 (37.4)		
Education		7.616 (5)	0.268
Primary	7 (3.7)		
Lower secondary	28 (14.7)		
Upper secondary	74 (38.9)		
College/Diploma	67 (35.3)		
University	12 (17.4)		
Professional	2 (2.8)		

* Mann–Whitney Test.

Table 5
The detection rate of the screening tools and number of cases detected in the second stage screening.

Positive and false positive cases following second stage screening				
	GHQ	SQ	GHQ + SQ	Total
Positive	1	14	14	29
False positive	19	103	39	161
Total	20	117	53	190
Detection rate and diagnosis of the detected cases				
Detection rate (%)	5	12	26.4	
BLIPS/APS	0	4	5	9
STAPS/STBLIPS	1	10	9	20
Total	1	14	14	29

our previous studies involving smaller sample size that both the SQ and GHQ-12 had low sensitivity (Razali et al., 2011). The detection rate of the SQ is 12%, which is higher than the GHQ (5%). When both the SQ and GHQ were positive, the chance to detect a positive case is much higher (26.4%). The GHQ-12 alone is not suitable for screening early psychosis; thus it should be combined with other screening instruments. The GHQ is rarely used in the study of early psychosis. In our review we found that, Morrison et al. (2002) incorporated the GHQ-28 (Goldberg and Hillier, 1979) with other instruments to assess general at-risk mental state to define caseness.

The use of more than one instrument in the screening will help clarifying the relation between symptoms targeted by the different instruments (Olsen and Rosenbaum, 2006). Among the variables measured in this study, the progress to the second stage of study was only influenced by individuals' genetic status. Surprisingly, a significantly higher number of general individuals progressed to the second stage as compared with individuals with genetic risk. As expected, the rate of false positive among them was high. There are few reasons explaining for the discrepancy of the scoring. At-risk subjects may underestimate their symptoms because of the unrealistic nature of their experiences and belief. While general individuals overestimate their symptoms or they could not differentiate between psychotic symptoms and normal experiences or interpreted them erroneously (Lincoln et al., 2010; Bell et al., 2007). The other reason we had observed that some general individuals purposely aggravated their symptoms in order to continue with the second stage of the study.

We found that the rate of false positive was high (85%) in the second stage assessment, which reflected the weakness of the SQ; interestingly, a greater number of general individuals than the relatives at risk proceeded to the second stage. This suggested that general population screening for psychosis risk, using a self-report questionnaire could result in a high false-positive rate. Thus, a clinical assessment or re-interview following a self-report questionnaire should be mandatory to eliminate false positive individuals as implemented in this study. This is consistent with the finding of the previous studies and suggestions by the others (Hanssen et al., 2003; Kendler et al., 1996).

5. Limitation

The main limitation of this study is the weakness in the sampling. The convenience sampling is considered as a weak sampling method. This study needs universal sampling for proper document of the prevalence. The SQ seems to have low sensitivity which contributed to higher percentages of false positive cases in the second stage. The specificity of the scale was also not satisfied. This could be overcome by reassessment of selective negative cases based on the initial screening, which had not been done in this study. Other approach to improve the detection rate is applying two different scales which is complementary to each other, providing criteria to detect different prodromal stages separately; late prodromal base scale (APS approach) and early prodromal base scale (BSs approach). It is also important to follow up the positive cases, especially among the at-risk family to assess their progression to psychosis. However, this is beyond the scope of this study.

6. Conclusion

A two-stage study is an effective and economical approach to detect asymptomatic individuals with a known risk factor. About 4% of the samples were positive for sub-threshold psychosis and the prevalence was higher in subjects at genetic risk. The success of screening programs much depends on the sensitivity and specificity of the screening tools. Low detection rate found in this study is partly related to poor validation indexes of the SQ and the sampling weakness. Since it is almost impossible to have a screening instrument with perfect validation indexes, clinical examination or reassessment of the positive cases and selective negative cases in the second stage should be mandatory. For detection of subjects in prodromal stage of psychosis, in order to improve detection rate it is better to use two different scales which is complementary to each other, providing criteria to detect different prodromal stages, late and early prodromal.

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