ORIGINAL ARTICLE

Clinical aspects of super-refractory schizophrenia: a 6-month cohort observational study

Aspetos clínicos da esquizofrenia super-refratária: estudo observacional de coorte com seguimento de seis meses

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Abstract

Objective: *Approximately 30% of treatment-resistant schizophrenic patients do not fully respond to Clozapine and such patients are termed Clozapine non-responders or super-refractory schizophrenics. The aim of this study was to characterize patients with super-refractory schizophrenia according to demographic and psychopathological variables, as compared with patients with refractory schizophrenia or non-refractory subjects.* ***Method:*** *One hundred and two outpatients meeting DSM-IV criteria for schizophrenia were followed-up for 6 months. Subjects were classified into 3 groups: non-refractory (n = 25), refractory (n = 43) and super-refractory (n = 34). Psychopathology was assessed by the Positive and Negative Syndrome Scale, the Schedule for Deficit Syndrome, the Calgary Depression Scale and the Quality of Life Scale. Patients were rated at 2-month intervals.* ***Results:*** *Higher levels of severity at the disease onset as well as higher severity of positive symptoms were found to be predictive of super-refractoriness.* ***Conclusions:*** *The super-refractory schizophrenia patients have psychopathological predictive factors that need studies comparing brain images, genetical features and other clinical comparisons.*

Descriptors: *Schizophrenia; Schizophrenia/therapy; Treatment outcome; Psychopathology; Refractory period/psychological*

Resumo

Objetivo: *Cerca de 30% dos pacientes de esquizofrenia resistentes ao tratamento não respondem completamente à clozapina. Esses pacientes são denominados não respondedores à clozapina ou portadores de esquizofrenia super-refratários. O objetivo deste estudo foi caracterizar pacientes com esquizofrenia super-refratária de acordo com as variáveis demográficas e psicopatológicas, em comparação com pacientes com esquizofrenia refratária e indivíduos não refratários.* ***Método:*** *Cento e dois pacientes ambulatoriais que preenchiam os critérios do DSM-IV para esquizofrenia foram acompanhados durante seis meses. Os indivíduos foram classificados em três grupos: não refratários (n = 25), refratários (n = 43) e super-refratários (n = 34). A psicopatologia foi avaliada pela Escalas de Síndrome Positiva e Negativa, pelo questionário para a Síndrome Deficitária, pela Escala de Depressão de Calgary e pela Escala de Qualidade de Vida. Os pacientes foram avaliados em intervalos de dois meses.* ***Resultados:*** *Encontrou-se que índices mais elevados de gravidade no início da doença, bem como maior gravidade dos sintomas positivos foram preditivos de super refratariedade.* ***Conclusões:*** *Os pacientes com esquizofrenia super-refratária apresentam fatores preditivos psicopatológicos que necessitam maior investigação em estudos de imagens cerebrais, características genéticas e outras comparações clínicas.*

Descritores: *Esquizofrenia; Esquizofrenia/terapia; Resultado do tratamento; Psicopatologia; Período refratário psicológico*

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Introduction

It has been clearly established that 30-60% of patients with the diagnosis of schizophrenia do not adequately respond to treatment with antipsychotics, and are defined as having Treatment Resistant Schizophrenia (TRS). Generally TRS is defined by an algorithm[1] which comprises 3 aspects: 1) no period of good functioning in the previous 5 years; 2) high levels of psychopathology as measured by the BPRS; and 3) no previous response to 3 periods of treatment (with antipsychotics of 2 different chemical classes) plus an additional failure to respond to a 6-week trial with haloperidol up to 60 mg/day.

Compelling evidence derived from systematic reviews[2] and meta-analyses[3] have established that Clozapine is the drug of choice for TRS but it is known that approximately 30% of patients with TRS do not fully respond to Clozapine treatment. Such patients are known as Clozapine resistant, incomplete responders[4] or having Super Refractory Schizophrenia (SRS).[5]

Patients with SRS have been the subject of a number of studies, mainly through small clinical trials where several Clozapine augmentation strategies were tested, such as association with antipsychotics, antidepressants or mood stabilizers.[4-6] However, the main mechanism that underlies SRS remains largely unknown, and only a few studies have addressed this issue using different methodological perspectives.

SRS is poorly defined in clinical terms although some predictors of treatment response to Clozapine have been described such as high levels of symptoms, higher extrapiramidal (EPS), a greater decrease of EPS during treatment, an early (but also late) age of onset as well as the paranoid subtype of schizophrenia.[7]

From the pharmacogenetic perspective, some studies of the pharmacokinetics of Clozapine response have shown that genetic variations in enzymes CYP1A2, CYP3A4 and CYP2D6 may play a role in the efficacy of Clozapine. However, most of the studies have focused on the pharmacodynamics of Clozapine and found that an inadequate response was significantly associated with the polymorphisms of certain receptor genes such as D3, $5HT_{2A}$, $5HT_{2c}$, $5HT_6$[8] and, more recently, also D1.[9]

Three studies on structural neuroimaging consistently found an increased prefrontal sulcal prominence to be associated with a poorer response to Clozapine.[10-12] However, two MRI studies showed no association between brain abnormalities and treatment response to Clozapine,[13,14] but a recent MRI volumetric study did show that larger right prefrontal gray matter volume was associated with a favorable response to Clozapine.[15]

In terms of functional neuroimaging, diminished cortical metabolism, particularly in the pre- frontal region, was found to be associated with poor response to Clozapine in a SPECT study,[16,17] whilst in a recent PET study, patients who were poor responders to Clozapine (less than 30% of improvement in the BPRS) had diminished cortical metabolism, predominantly in frontal areas.[9]

Recently, we have presented preliminary data on neuropsychological aspects comparing patients with SRS to patients with TRS and it was found that SRS patients presented worse performance than patients with TRS. However, the sample size was too small to detect significant statistical differences.[18] Actually, the drawback with the majority of pharmacogenetic studies with Clozapine, as well as most of the studies summarized above, is their inability to detect the extent of effects, due to small sample sizes.[19] Moreover, to date only one study has found a correlation between pharmacogenetic data with neuroimaging parameters.[9] Thus, there is a paucity of data regarding super-refractory schizophrenic patients which have still not been adequately studied, especially in terms of demographic and psychopathological aspects. Such an investigation is necessary to establish predictive factors of response to Clozapine. Therefore, in the present study we aimed to characterize super-refractory patients in terms of demographic and psychopathological aspects as compared with refractory and non-refractory cases through an observational study of a cohort of outpatients with the diagnosis of schizophrenia at the Institute of Psychiatry of the Universidade de São Paulo.

Patients and method

We conducted a 6-month cohort study with patients undergoing pharmacological treatment for schizophrenia. We compared demographical and clinical aspects of three groups: schizophrenic patients who responded to other antipsychotics than Clozapine, Clozapine responders (refractory patients), and Clozapine non-responders (super-refractory patients).

1. Patients

All patients were recruited at PROJESQ-Schizophrenia Program of the Institute of Psychiatry of the Hospital das Clínicas of the Universidade de São Paulo Medical School (FMUSP). An outpatient clinic was specially created for this project where 102outpatients aged 18 to 65 years and who met DSM-IV criteria for schizophrenia were enrolled in the study. Refractoriness was defined according to criteria established by Kane et al., which include poor response to at least two conventional antipsychotics for at least 6 weeks each with doses corresponding to 20 mg/day or more of haloperidol, or 1000 mg/day of chlorpromazine.[1] Lack of response was defined as lack of improvement of at least 20% of the BPRS scores and the lack of reduction in the CGI of at least 3 points.

Patients who met the criteria for refractoriness received Clozapine and those who did not improve after 6-months' treatment with Clozapine, i.e. maintained persistent psychotic symptoms, were then classified as super-refractory.

Patients who responded to antipsychotics other than Clozapine were defined as responders or controls.

This was a cohort study in which, at the time of enrollment, all patients were already undergoing treatment according to their clinical condition, be it refractory, control or super-refractory.

Pharmacological treatment was administered in naturalistic conditions, with the treating physicians changing medication dosages at their own discretion. Refractory patients received Clozapine at doses ranging from 300 to 900 mg daily usually in monotherapy, although some of them used benzodiazepines, anticonvulsants (due to Clozapine-induced seizure) or antidepressants. Super-refractory patients were often under politherapy, i.e. combination of clozapine and another antipsychotic.

Patients with neurological diseases such as epilepsy or encephalopathy, mental retardation, non-stable clinical diseases, risk of pregnancy, history of non-compliance, or alcohol and illicit drug abuse were excluded from the study. The present study was conducted in compliance with the Declaration of Helsinki and its amendments, and was approved by the institutional ethical committee.

Table 1 - Demographic characteristics at baseline; * N = 22, **N = 42;*N = 31**

Characteristic		Control	Refractory	Super-refractory	p
n		25	43	34	
Age (years)		37.84 (12.3)	37.31 (8.28)	37.33 (11.16)	0.976
Age of onset		21.17 (7.15)	19.39 (4.73)	20.55 (5.66)	0.921
Age of first hospitalization		14.25 (18.98)	17.32 (19.17)	23.99 (17.9)	0.908
Gender	Male	14	30	18	0.313
	Female	11	13	16	
Race	White	20	29	31	0.424
	Black	3	8	0	
	Asian	2	5	3	
	Other	0	1	0	
Marital status	Single	22	41	33	0.397
	Married	5	2	1	
	Divorced	1	0	0	
Education (years)		10.32 (2.92)	9.83 (3.13)	10.81 (3.80)	0.407
Mean duration of disease (years ± SD)		*14.6 (10.11)	**17.74 (7.72)	***16.65 (9.27)	0.638
Mean number of psychiatric hospitalizations		2.08 (2.32)	2.73 (2.43)	3.24 (3.03)	0.785

Test used: Anova test with post hoc test for Age, age of onset, age of first hospitalization, education, mean duration of disease and mean number of psychiatric hospitalizations. Chi square test Yates correction for gender, "race" and marital status with.

2. Method

Patients were assessed 4 times during the 6-month study period, with 8-week intervals between assessments. At the beginning of the study, demographic and general clinical features such as age, age of onset of schizophrenia, gender, ethnicity, duration of the illness, number of hospitalizations, age of first hospitalization, comorbidity with other relevant medical diseases and substance abuse were collected. Psychopathological data were assessed using scales which included the Brief Psychiatric Rating Scale - anchored version (BPRS-A),[20] the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression (Guy), the Calgary Depression Scale for Schizophrenia, the Quality of Life Scale and the Schedule for Deficit Syndrome (SDS). The analysis of psychopathology was also performed using cluster symptoms as derived from BPRS-A.[21]

Raters were trained in the use of assessment scales prior to the beginning of the study reaching reasonable reliability (Intra-Class Correlation mean average for all scales: 0.72; p = 0.001). Groups were compared in terms of antipsychotic doses using their respective chlorpromazine equivalents as proposed by Woods.[22]

The SPSS 12.0 statistical package was used to analyze the data. The significance level was set at 0.05. When appropriate, parametric and non-parametric tests were used for analyses of demographic data. Means (± SD) were compared by Analysis of Variance (ANOVA) with post-hoc Scheffe for multiple comparisons. The significance level in all analyses was 0.05 (2-tailed). Chi square tests were used to analyze the variables race, marital status and gender and Yates correction was applied when necessary.

This study has been approved in according to Research Ethical Commite of Hospital das Clínicas of the Universidade de São Paulo Medical School, under number 402/02, under presidence of Dr. Jorge Kalil Filho in 2002/june/27th.

Results

Of the 102 patients, 25 (24.5%) were classified as responders, 43 (42.2%) being refractory (Clozapine responders) and 34 (33.3%) super-refractory.

The mean chlorpromazine equivalents of the Responders group were 266 mg (sd = 145) at the beginning of the study and 248 mg (sd = 83.5) at the final observation. In the Refractory Group the mean chlorpromazine equivalents were 975 mg (sd 232 mg) at baseline and 475 mg (sd 329 mg) at the end of the study, while in the Super Refractory Group the mean chlorpromazine equivalents were 1016 mg (sd = 204 mg) at baseline and 770 mg (sd 210,9 mg) at the endpoint.

Overall, by Anova (to continued variables) and chi-square tests (to dichotomic variables) no demographic differences were observed between the three groups. The mean age was 37 years (± 3.8) across groups. Most patients were males (60.8%) and the mean age at onset of the disorder across groups was 20.7 years (± 5.9) while the mean age at first hospitalization was 22 years (± 4.8). Educational levels also did not differ between groups. Table 1 summarizes demographic characteristics.

The three groups did not differ regarding number of re-hospitalizations during the study.

The super-refractory group had the highest scores for totals of BPRS ($p < 0.001$ in all visits, Figure 1) and totals of PANSS ($p < 0.001$ in all visits, Figure 2) when compared with refractory and control groups on the 4 visits (V0, V1, V2 and V3). Positive and Negative PANSS subscales (Tables 2 and 3) also showed differences in all four visits. In all analyses Anova followed by a Post Hoc test was performed. High scores in PANSS and BPRS were observed in all visits (Tables 2 and 3 and Figures 1 and 2).

Table 2 – PANSS Positive subscale - mean scores and comparative analyses among groups

Time	Control (n = 25)	Refractory (n = 43)	Super-refractory (n = 34)	F	p
Baseline	12.52	16.85	22.18	6.966	< 0.001
8 weeks	11.16	16.86	19.73	12.68	< 0.001
16 weeks	11.75	15.70	22.24	11.36	< 0.001
24 weeks	10.45	15.41	23.36	15.58	< 0.001

Table 3 – PANSS Negative subscale - mean scores and comparative analyses among groups

Time	Control (n = 25)	Refractory (n = 43)	Super-refractory (n = 34)	F	p
Baseline	16.84	23.98	24.67	2.236	0.004
8 weeks	16.76	24.14	23.40	1.309	0.005
16 weeks	15.88	23.44	24.38	4.060	0.001
24 weeks	16.64	21.49	24.32	1.755	0.021

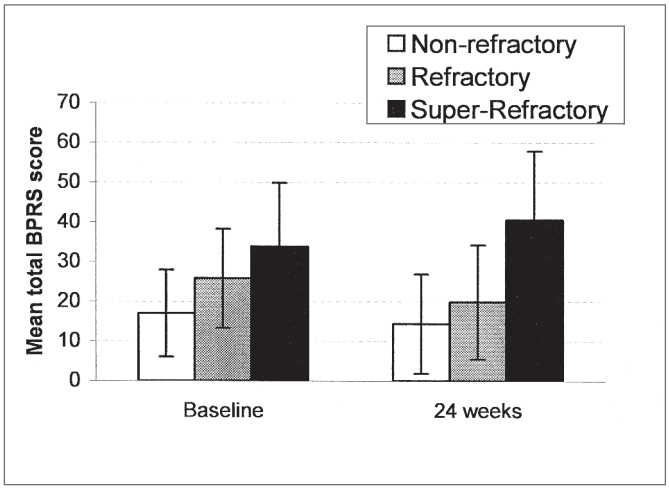

Figure 1 - Mean total BPRS score at baseline and at 24 weeks

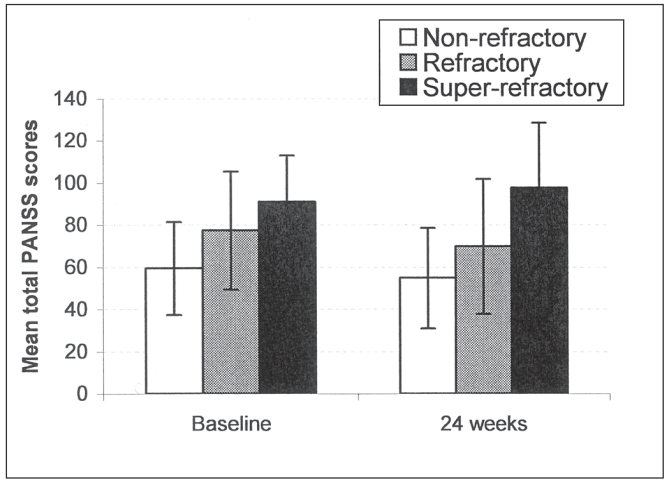

Figure 2 - Mean total PANSS scores at baseline and at week 24

The super-refractory group had the worst scores on both CGI scales (Severity and Improvement) ($p < 0.001$ in all visits - V0, V1, V2, V3, according to ANOVA and post hoc test). Refractory and control groups showed a trend of improvement at endpoint, whereas the super-refractory group showed no improvement at all according to total PANSS and total BPRS scores (Figures 1 and 2).

The Deficit Syndrome Scale showed similar differences, reflecting the worse baseline condition of the super-refractory group. There were no changes in SDS scores throughout the observation period.

The Calgary Depression Scale for Schizophrenia scores showed no statistical significant differences between groups on the 4 visits by means of Anova test and post-hoc: ($p= 0.106$ on V0; $p = 0.566$ on V1; $p = 0.971$ on V2 and $p = 0.248$ on V3). The results from the assessment of Quality of Life showed that, in average, the super-refractory patients had lower means than the other two groups. QoL score evaluated in the final visit showed differences between groups (Table 4). The control group showed an improvement of 9.98% on QoL score at the endpoint while the other two groups show less significant improvement.

Discussion

To date, only a few studies have addressed the characteristics of patients with super-refractory schizophrenia.

Although some characteristics have been described as predictors of refractoriness, namely age of onset of disease, male gender and number of hospitalizations,[12,23-26] the present study found no specific predictors of super-refractoriness. Interestingly, there were no demographic differences between refractory and super-refractory subjects, and despite the greater disease severity of super-refractory patients, they did not differ in terms of number of hospitalizations in comparison to refractory cases.

In the present study Refractory patients (Clozapine responders) remained stable i.e, without showing improvement in terms of psychopathology throughout the observation period, despite adequate Clozapine treatment. This is opposed to the study of Kane et al. who found that refractory patients had a better improvement with Clozapine than patients under haloperidol treatment.[27] In our study, the severity of illness was in fact associated with super-refractoriness, which is in accordance with some studies.[7]

It is interesting to know that in terms of Quality of life measures although the super-refractory group had the lowest QoL scores, this group had an improvement of 2.5% in QoL scores but such improvement did not correlate with improvement in psychopathology. Additionally, this may be related to the fact that patients were stimulated by the health care team to engage in more physical and social integration activities.

The conclusions of the present study are limited due to the fact that this is an observational and not a controlled study. Patients with super-refractory schizophrenia did not differ from refractory patients in terms of their demographical characteristics but differed due to higher severity of illness, and a higher score of positive symptoms which were found to be predictive of super-refractoriness. Further controlled studies including neuroimaging and genetic evaluations are warranted to identify predictive factors of super-refractoriness.

Table 4 – Mean QoL scores and comparative analyses among groups

Time	Control (n = 25)	Refractory (n = 43)	Super-refractory (n = 34)	F	p
Baseline	66.58	53.50	48.73	0.037	0.035
8 weeks	69.71	50.17	50.29	0.235	0.009
16 weeks	71.75	52.50	49.93	0.01	0.003
24 weeks	72.95	53	49.96	2.010	0.003

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