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KRAEPELINIAN SYSTEMATIC PARAPHRENIA AS A RECOGNIZABLE DISORDER

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Abstract: *Objectives:* To demonstrate that systematic paraphrenia as defined by Kraepelin (the most consistent prototypic paraphrenia subtype) can be recognized and diagnosed. *Subjects and methods:* All patients admitted to a Portuguese psychiatric inpatient unit between September 2006 and October 2011, meeting the criteria for systematic paraphrenia based on Kraepelin's definition, Munro's operational criteria and the authors' criteria, were evaluated by two senior psychiatrists. *Results:* Out of 27 evaluated patients, 16 (10 women and 6 men) were confirmed as having systematic paraphrenia, accounting for 0.83% of the total number of inpatients (1921). The mean age of onset was 34.3 years (SD = 8.9) and the mean duration of illness at observation was 19.5 years (SD = 12.3). Most (n = 13) had no family psychiatric history, were married (n = 11) before the onset of the disorder and none had previous sensorial deficit. Six were born outside of Portugal. Their academic achievements were only slightly inferior to the general population. *Conclusions:* Systematic paraphrenia can be recognized and diagnosed. Contrary to Kraepelin, the disorder seems to be more frequent in women. It does not seem to be associated with old age or heredity. This syndrome is internally consistent and its only similarity with schizophrenia is the positive symptoms' dimension. It should also be distinguished from late paraphrenia.

Key words: Schizophrenia, dementia praecox, paraphrenia, systematic paraphrenia, chronic hallucinatory psychosis.

Introduction

Emil Kraepelin (1856-1926) defined paraphrenia in the 8th edition of his textbook (1) but since then, except for the closely linked francophone "chronic hallucinatory psychosis" (CHP), the concept was almost forgotten. Patients with this disorder were mostly diagnosed as having schizophrenia, paranoia, schizoaffective disorder, psychosis not otherwise specified (PNOS) or late-life psychosis. In our view, some patients with chronic psychotic symptoms since young adulthood without deteriorating course, semi-systematized delusions or affective symptoms seem to fit a mostly homogeneous group. However, given the overinclusive and overlapping nature of some criteria of current classifications, patients with paraphrenia have been dispersed throughout several diagnostic entities. These reasons prompted us to determine the possibility of recognizing patients with systematic paraphrenia.

Historical background

Kraepelin described a small group of chronic psychotic patients (with odd delusions and hallucinations) similar to patients with dementia praecox, but in which the harmony of psychic life was much less affected or, at least, only on certain intellectual functions and called it "paraphrenia", with four subtypes: systematic, expansive, confabulatory and fantastic. In paranoia, the existence of completely systematized delusions, without prominent hallucinations, allows for the differential diagnosis with paraphrenia (1). Systematic paraphrenia is defined by Kraepelin as a disease with "extremely insidious development of a continuously progressive delusion of persecution, to which are added later ideas of exaltation without decay of the personality" (1). It usualy starts with unspecific prodromal symptoms and has a fluctuating course and phasic development (1). Then, delusional persecutory ideas come into sight, followed some years later by hallucinations (any modality), at which point ideas of thought and will control and confabulations may also be present. Finally, grandiose delusional ideas usually appear. Mood typically changes:

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in the beginning, anxious and depressive, later becoming hostile and finally excited. There is no affective flattening. Daily activities are affected only to the extent of their relation to the psychotic symptoms. In Kraepelin's data, 60% were men and most (> 50%) had an onset between 30 and 40 years (1). Heredity didn't seem to play an important role. Personality preservation was the most important factor differentiating it from the kraepelinian concept of "paranoid dementia" (which partially fits the broader concept of paranoid schizophrenia).

In what concerns to the other subtypes, Kraepelin stated that expansive and confabulatory paraphrenias were difficult to differentiate from manic-depressive disorder. He stated the same for fantastic paraphrenia in relation to dementia praecox.

In 1911, with the word "schizophrenia", Eugen Bleuler (1857-1939) considered that a dementia evolution was not required for the diagnosis, and henceforth paraphrenias fell into the schizophrenia field (2). In 1921, Wilhelm Mayer reviewed 78 of Kraepelin's patients with paraphrenia and concluded that 42 had schizophrenia (3). Seventeen patients with systematic (in 45), and 6 with confabulatory confabulatory paraphrenia (11) remained as representatives of the "kraepelinian concept of the disease" and the remaining were rediagnosed with other psychosis. Those 17 patients with systematic paraphrenia had developed the disease late in life, which led him to conclude that this disease could represent a kind of late-life dementia praecox (3). He ignored the fact that, at least 23, at least 23 (in 78 patients) maintained the diagnosis.

As Berrios said, this paper over time was probably overemphasized (4). So, during the 20th century most authors forgot the paraphrenia concept. When invoked, however, the late onset of the disease was always underscored. This position was reinforced by M. Roth and J. Morrissey in 1952 with the "late paraphrenia" concept (5, 6). Other authors, however, concluded that the syndrome was poorly defined and clinically heterogeneous (7, 8).

Karl Leonhard's paraphrenia concept is somewhat dissimilar. He distinguished between systematic schizophrenias (with permanent defect and centrally compromised personality) and unsystematic schizophrenias (which allowed for remissions). Within unsystematic schizophrenias Leonhard placed the affective paraphrenia in which some forms would resemble Kraepelin's concepts of systematic paraphrenia and paranoia (9).

According to the current classifications (DSM IV-TR and ICD-10), patients with paraphrenia would fall into diverse categories (10, 11).

In 1991, Munro, based on Kraepelin's descriptions, developed operational criteria for the diagnosis of paraphrenia (12).

Table 1
Alistair Munro et al. operational criteria for paraphrenia

Operational Criteria For Paraphrenia (12)	
A delusional disorder of at least 6 months' duration	Preoccupation with one or more semi-systematized delusions, often accompanied by auditory hallucinations. These delusions are not encapsulated from the rest of the personality The affect remaining notably well preserved and relatively appropriate. Even when severely disturbed the patient shows an ability for rapport with others and considerable affective warmth which is not typical in any form of schizophrenia. Understandability of disturbed behaviour as being related to the content of the patients's delusions and hallucinations Only partially meets Criterion A for schizophrenia
Exclusion criteria	Intellectual deterioration Visual hallucinations Incoherence Marked loosening of associations Flat or grossly inappropriate affect Grossly disorganized behaviour Significant organic brain disorder

Using Munro's criteria, Ravindran et al. (13) recruited "atypical" psychotic patients assessed by structured interviews from two hospitals, over a period of 18 months. They identified 33 patients with paraphrenia and concluded that it was a recognizable disorder, not linked to old age, predominant in women (24 out of 33) and not related to heredity. No further studies on paraphrenia have been performed ever since. A somewhat overlapping concept would be CHP, defined by G. Ballet (1853-1916), as a psychosis triggered by hallucinations, with late deterioration (if any). He described that it was predominant in men (7:5). (14, 15) An historical perspective shows that chronic hallucinatory psychosis, paraphrenia and paranoid schizophrenia are closed concepts, the development of which expresses many reciprocal influences (16, 17).

However, because of its unstable definition, ranging from a pure hallucinatory disorder to the likeness of Kraepelinian paraphrenia, we must examine its studies with caution (18). Some studies concerning CHP, however, like that of Dubertret et al., might carry important data (19). Actually, Dubertret's criteria for CHP (based on Pull and Pichot's works) were in fact very close to Kraepelin's definition of paraphrenia (20, 21), in line with J. Guelfi's opinion (22).

In Dubertret's work, all 38 CHP patients were women and had lower negative and positive symptom scores when compared with groups of women with schizophrenia. CHP patients had significantly higher Global Assessment of Functioning scores at discharge and less affective flattening (5%). CHP patients had less frequently a family history of shizophrenia, a 25 years

higher age of onset and did not show progressive cognitive deficits. In 2006, Mauri et al. studied 9 patients (7 women and 2 men) with "hallucinatory disorder" and found that they had fewer negative and disorganized symptoms when compared with patients with schizophrenia (23).

The aim of the present study was to test the feasibility of recognizing and diagnosing patients with systematic paraphrenia (case-finding study), singled out by Kraepelin as the most consistent subtype of the entity.

Methods

From September 2006 up to October 2011, 1921 patients were consecutively admitted to a 29-bed general hospital psychiatric inpatient unit (catchment area of 350,000 inhabitants) located near Lisbon, Portugal. During that period the permanent staff of four psychiatrists performed an active screening for patients likely to fulfil the diagnosis of systematic paraphrenia (defined according to Kraepelin's and Munro's operational criteria) (12, 13, 24). In addition to Munro's criteria we required a disorder duration of at least 5 years, so that cognitive deterioration could be assessed and schizophrenia misdiagnosis avoided (25–27). To isolate systematic paraphrenia, we also excluded all patients with prominent affective symptoms as well as confabulatory or fantastic delusion predominance. A head CT was performed in patients older than 45 years to exclude organic disorders. Patients were subsequently re-evaluated by a second psychiatrist. Both assessments took place immediately before discharge. The patients were included in the systematic paraphrenia group only when there was unequivocal agreement between the two psychiatrists. Otherwise, patients were attributed a diagnosis according to the ICD-10 (11).

Clinical, demographic and social variables were collected in all patients and are listed below.

Ethics approval of the study was obtained from the institutional ethics review board. All participants gave informed consent.

Results

Each of the twenty-seven patients was assessed by two of the four senior psychiatrists as likely candidates for the systematic paraphrenia diagnosis. Of these, 16 (10 women and 6 men) met criteria for systematic paraphrenia (SP) by both investigators (0.83% of all acute patients), which corresponds to an inter-rater reliability of 0.59. The remaining patients were classified as follows: schizophrenia [F20.x] (n = 3), delusional disorder [F22.0] (n = 3), schizoaffective disorders [F25.x] (n = 3) and bipolar affective disorders [F31.x] (n = 2). Their mean age was 50.1 (SD = 11.3) (53.2 for women and 46.4 for men).

Table 3
Age of onset of patients with systematic paraphrenia (n=16)

Age of onset (yrs.)	Total (%)	Women	Men	Cumulative (%)
10-19	1 (6.25%)	0	1	1 (6.25%)
20-29	3 (18.75%)	2	1	4 (25%)
30-39	9 (56.25%)	6	3	13 (81.25%)
40-49	2 (12.5%)	1	1	15 (93.75%)
50-59	1 (6.25%)	1	0	16 (100%)

Table 2
Socio-demographic and clinical variables

Demographic Variables	Time of evaluation	Scale/Criteria
sex and country of birth	----------	
age	at inception and at admission	
marital status	at inception and at admission	married or other (divorced, widowed, single)
education level	at admission	elementary school (≤ 4 years), middle school (≥ 5 and ≤ 9 years), high school (≥ 10 and ≤ 12) and university
Clinical Variables	**Time of evaluation**	**Scale/Criteria**
illness duration	at admission	
Schneider's first-rank symptoms	at admission	yes or no
non-prominent affective symptoms	at admission	yes or no
first-degree family history of psychiatric disorders	at admission	yes or no
social and occupational functioning	at admission and prior to the disorder onset	evaluated both qualitatively and using the Social and Occupational Functioning Assessment Scale (SOFAS),(28) ranging from 100 (superior functioning) to ≤ 50 (serious impairment)
sensory deficits	prior to the disorder onset	yes or no
response to pharmacological treatment	before the discharge	resistance was defined as absence of clinical response after two trials using different second-generation antipsychotics in monotherapy, each with a duration of 4 to 6 weeks (29)
treatment adherence	since the last admission (if any) and confirmed with the local mental health teams	total adherence, occasional missings or dropped-out

The mean results of the systematic paraphrenic group can be seen in table 4.

Table 4
Characterization of patients with systematic paraphrenia (n=16)

Sistematic Paraphrenia	Results
Age at admission	53.8 (SD = 9.8) (55.4 women and 51.2 for men)
Age of onset	34.3 (SD = 8.9)
Illness duration (years)	19.5 (SD = 12.3)
Country of birth	Portugal - 10 patients Mozambique - 2 patients Cape Verde - 1 patients Guinea-Bissau - 3 patients
Marital status at onset of the disease	Married - 11 patients Other - 5 patients
Marital Status at admission	Married - 4 patients Other - 12 patients
Education level	elementary school - 7 patients, middle school - 5 patients, high school - 2 patients, university - 2 patients
Family history in first-degree relatives	3 patients (unspecified)
Sensorial deficits preceding onset	0 patients
Schneider's first-rank symptoms	10 patients (thought broadcasting - 5, third-person hallucinations - 5, passivity - 4, somatic hallucinations - 1, écho de la pensée - 1)
Affective symptoms (non-prominent)	3 patients
treatment adherence (n= 13)	fully complied - 3 patients occasional missings - 4 patients dropped out - 6 patients
Treatment resistance	3 patients (all woman)
Qualitative evaluation of social performance	no decline - 9 patients (56.3%) overall worsening - 7 patients (43.8%)
SOFAS (mean score)	decreased +/- 25%(from 79.7 to 59.7) - 14 patients maintain score - 2 patients

Below we will point out additional data.

The mean age of onset in the SP group was 34.3 (SD = 8.9 years), ranging from 18 to 57 (35.7 years for women and 32 for men). The illness duration at observation was on average 19.5 (SD = 12.3 years).

Eleven patients were married at illness onset (of which 4 became divorced, 3 widowed and 4 remained married). None of the divorced/widowed ever remarried. No patients who were single or divorced before the onset eventually married.

Evaluation of treatment adherence was only possible in 13 patients, as 3 did not have any previous admission.

When compared with treatment responders, resistant patients were older (mean age 62.0 vs. 48.6 years) and had been ill for a longer period of time (29.6 vs. 16.6 years), but they did not differ on the mean age of onset (32.3vs. 32.9).

In the qualitative evaluation of social performance, from the 11 patients who were initially well, 6 did not present any decline, while 5 did. From the 5 (31.2%) patients that already had a deficit in social performance prior to the onset, with a reduced social network (limited to first-degree family members), 3 exhibited no decline and 2 eventually reached total social isolation.

Table 5
Employment status of patients with systematic paraphrenia (n=16)

Work status before onset	Work status at observation	Women	Men	Total (%)
Unemployed	Unemployed	0	1	1 (6.25%)
Employed	Unemployed	5	3	8 (50%)
Employed	Employed	2	2	4 (25%)
Employed	Retired	3	0	3 (18.75)

Discussion

This study lends support to the idea that it is possible to isolate a subgroup of patients with systematic paraphrenia. The inter-rater reliability of 0.59 between the two observers is not far from the number reported in papers that investigated this coefficient in psychotic disorders (30). Most selected patients were women and with a good track record of relationship and educational levels. The diagnosis was not age related and there was no preceding sensorial deficit or any signs of deteriorating evolution. Migrant status may be a risk factor. It is worth mentioning that no patient diagnosed with SP was readmitted during the study, which may provide support for its favourable outcome.

The number of patients recruited was lower than in Ravindran et al.'s study (13). Direct comparison is difficult because the catchment area population and number of evaluated patients are not disclosed and we excluded other paraphrenia subtypes.

Data is sparse for considerations about paraphrenia's prevalence and its relation with schizophrenia. In our study, SP accounted for 0.83% of all patients and 0.59% of admissions. In Mauri's study, hallucinatory disorder represented 0.34% of all inpatients and outpatients evaluated (the mixed sample could account for the lower prevalence) (23). It is quite possible that social integration of SP patients could account for the diagnosis of the disorder mainly in periods of acute exacerbations, allowing for a larger number of patients to remain undetected in the community.

Ravindran's data showed that in most patients (>80%) the disorder began before the age of 49 (13). Similarly to this author, and to Mauri's and Kraepelin's data, we found an earlier onset. Nevertheless, there was still a later onset compared with patients with schizophrenia. (1, 19, 23) Assuming that Pull and Pichot's CHP diagnostic criteria (20, 21) include the patients selected by Munro's criteria, we found a mean age of onset (34.3; range 18-57)

nearly 15 years younger than in Dubertret's study. There was no correlation between age of onset and gender in our study. Women were overrepresented in our sample (62.5%), contrasting with male predominance in Kraepelin's and Ballet's data (1, 14). Ravindran's and Mauri's data also confirm the female predominance (77.7% and 72.7%) (13, 23). Dubertret's study enrolled only women (19).

Thirty per cent of Ravindran's patients were single at the time of evaluation (13), which is in line with our results (25%). The later onset of symptoms may help explain the fact that most patients were previously married (68.8%).

Migrant status as a predisposing factor has been reported in the literature (13). More than a third of our patients were immigrants, a factor that may play a role in the pathogenesis of the disorder, since it is clearly overrepresented when compared with local population. Ravindran's study also reported a high number of patients born outside Canada (42.9%) (13).

The systematic paraphrenia group's level of education was slightly lower than in the Portuguese general population (GP) (31). While none reported having no educational qualifications (as opposed to 10% of the GP), most (43%) were in the elementary level (vs. 28.4% in the GP). The rate of patients with high school level (13%) and a university degree (13%) was similar to that of the GP (15.7% and 11.9%, respectively). The small sample size, the use of unadjusted educational qualification rates and the large number of immigrants hinder these findings.

Thought broadcasting and third-person hallucinations were the most frequently elicited Schneider's first-rank symptoms, in contrast with schizophrenia, where auditory hallucinations of voices commenting or discussing predominate (32, 33). As in Ravindran's data we found no significant sensory deficits. In addition to previously discussed characteristics, these results suggest that late paraphrenia and systematic paraphrenia should be considered different clinical entities.

Another predisposing factor described by Ravindran was social isolation. This could be due to disruption caused by psychotic symptoms, but also to premorbid paranoid and schizoid personality traits, which occur more commonly in paraphrenia than by chance (13). At the age of onset, 5 (31.2%) patients already showed low social performance, and this had decreased in 7 (43.8%) at assessment. It is possible that long-standing untreated psychotic symptoms, and not neuropsychiatric deficits, can help explain this decline. In Ravindran's data, 57.1% of patients had social isolation prior to admission (13).

The mild decline in SOFAS scores is in line with Kraepelin's descriptions (1). Daily living, occupational activity and social functioning are likely to deteriorate during exacerbations, a view consistent with a non-deficitary evolution (13), which has treatment implications, namely from a psychosocial and rehabilitation perspective. Most of our patients were acutely ill for several months and gathered data was relative to that period of time. A small degree of decline may occur on account of long-standing psychotic symptoms and not necessarily due to the disorder's inherent tendency for intellective deterioration.

The fact that out of 15 previously employed SP patients only 4 remained at work underscores the burden of the disorder, but allows for a modicum of optimism when considering the prognosis and treatment plan.

About 50% had either partially or fully complied with medication. Although no direct comparisons can be made, on account of different designs and absence of structured evaluation of adherence, our data suggest a lower dropout rate than previously described for schizophrenia, namely in the CATIE trial (74% dropout rate at 18 months) (34). These findings are at odds with what we had anticipated. However, the low dropout rate was evaluated retrospectively. Preservation of intellectual functioning and better insight may be two possible reasons for this apparent better adherence.

Ravindran stated that clinical outcome is often satisfactory, with a complete return to close to normal (13). In our sample, resistance to treatment was documented only in female patients and there was no difference as to age of onset between resistant and non-resistant patients, both findings contrasting with schizophrenia (35). Although we did not perform a standardized evaluation of treatment response, we did find that only a fraction of our patients were resistant(19%), which is in line with Ravindran's data, in which 65.4% of patients had a good response to treatment, but in contrast with Mauri's statement that hallucinatory disorder patients rarely respond to treatment (13, 23).

Our study supports the lack of significant genetic load, in accordance with previous results. There is a low frequency of schizophrenia in families of patients with paraphrenia, suggesting little or no genetic association (13, 19). In Ravindran's study, psychiatric family history was found in 35.5% of patients, leading to the conclusion that its presence seemed to be associated with an earlier onset of paraphrenia (13).

Limitations

Even with Munro's operational criteria, the diagnosis of systematic paraphrenia is not consensual, as we managed to reach consensus agreement in 16 out of 27 patients. Our own supplementary criteria, stricter than previous studies (in order to isolate the systematic subgroup), may have contributed to alternative diagnosis formulation and hence diminish the number of included patients. Other limitations in our study include the small sample size, the absence of follow-up or control group, and the fact that no rigorous assessment of cognitive or

negative symptoms was performed. Additionally, the interviewers were not blind to the patient's possible diagnosis and most supported the hypothesis of systematic paraphrenia as a recognizable disorder.

Conclusions

This study lends support to the idea of systematic paraphrenia as a specific diagnostic entity that can be recognized and should be reclaimed. The age of onset is later than that usually found in schizophrenia but earlier than that of late paraphrenia and late-onset schizophrenia. As underscored by Kraepelin, the internal harmony of the psychic life and minor disorders of cognition, volition and emotion distinguish paraphrenia from schizophrenia.

The stability of systematic paraphrenia diagnosis should be assessed by long-term follow-up studies, with larger samples and making use of structured cognitive evaluation and better characterization of the negative syndrome, as well as having a matched control group of patients with schizophrenia.

The definition of this category as a separate entity from schizophrenia is fundamental for a better management of these patients, because their specific demands are quite different, both in psychosocial dimensions and prognosis. Moreover, it can allow the investigation of specific pharmacological treatments in more homogeneous groups. Additionally, this case-finding study presents itself as a contribution to the discussion regarding the upcoming DSM-5 and ICD11 diagnostic and classification systems and the place and role of possible sub-categories of 'schizophrenia spectrum' disorders.

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