The French concept of “psychose hallucinatoire chronique”—a preliminary form of schizophrenia?
The role of late-life psychosis in the anticipation hypothesis of schizophrenia

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The French concept of “psychose hallucinatoire chronique” (PHC or chronic psychotic hallucinations) is characterized by late-onset psychosis, predominantly in females, with prominent and frequent hallucinations, but almost no dissociative features. In the 1920s, de Clérambault stated that the syndrome of mental automatism specifically characterized this psychotic disorder. The distinction between schizophrenia and chronic delusional syndromes (such as paraphrenia and PHC) is currently used in France and was included in Pull and Pichot’s classification in the 1980s, although there are no international criteria for these syndromes (International Statistical Classification of Diseases, 10th Revision [ICD-10] or the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [DSM-IV]).

The nosographic status of the nonaffective/organic psychotic states arising in middle to late life has been surrounded by controversy and uncertainty. Both Kraepelin and the Sherman paradox describe the fact that multiplex families frequently have only one affected ascendant, meaning that an isolated sporadic case is at the origin of a highly loaded family. We thus propose that if unstable mutations are involved in the risk for schizophrenia, then PHC might represent a moderate disorder belonging to the schizophrenia spectrum phenotype.

Keywords: chronic psychotic hallucinations; “psychose hallucinatoire chronique”; familial risk; late onset; schizophrenia; risk factor

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and Bleuler\textsuperscript{10} described disease states resembling those with an early onset, but which began at a more advanced age in some cases. Nevertheless, in 1919, Kraepelin described the concept of “paraphrenia,” which did not have age boundaries, but rather distinguished a group of patients with primary delusional symptoms, preservation of personality, an impact on mood, and lack of deterioration, in contrast with dementia.\textsuperscript{11} In 1943, Manfred Bleuler coined the term “late-onset schizophrenia” to describe a particular group of patients with onset of psychosis after the age of 40 years and with less affective flattening and less formal thought disorder.\textsuperscript{12} These descriptions are reminiscent of Kraepelin’s paraphrenia with delusional syndrome and absence of disorganization or deterioration.

Since the early emergence of geriatric psychiatry in the 1950s, the European literature on schizophrenia-like symptoms with a late onset has been dominated by the diagnosis of late paraphrenia.\textsuperscript{13,10} In 1955, Roth defined late paraphrenia as “a well-organized system of paranoid delusions with or without auditory hallucinations existing in the setting of a well-preserved personality and affective response,” beginning after the age of 60 years.\textsuperscript{19} Late paraphrenia distinguished the illness from schizophrenia and emphasized its clinical similarities with Kraepelin’s paraphrenic patients. This concept was readily adopted and was included in ICD-9.\textsuperscript{20}

There is much debate in the literature as to whether late paraphrenia represents cases of late-onset schizophrenia with an age at onset of over 60 years or is a variety of disorders within which only a proportion of patients fulfill the diagnostic criteria for schizophrenia.\textsuperscript{15,17,21} Organic factors are often supposed to play an important role in the initiation and maintenance of psychotic symptoms in late-life psychoses.\textsuperscript{15,16,18,22,23} In a review, Harris and Jeste concluded that “late-onset schizophrenia is not a homogeneous entity but is a syndrome with clinically and biologically relevant subtypes.”\textsuperscript{24} The absence of clear boundaries between PHC, late-onset schizophrenia, and late paraphrenia leads to confusion and limits comparisons of the various research findings. The nosologic status of psychotic states arising in late life is still debated. Recently, the International Late-Onset Schizophrenia Group Consensus Conference produced sufficient evidence to recognize two illness classifications: late-onset schizophrenia (onset after age 40) and very-late-onset schizophrenia-like psychosis (onset after age 60).\textsuperscript{25}

In the USA, the DSM-III-R Advisory Group acknowledged the need to allow a separate category of “late-onset” for patients whose illness began after age 44. This decision was largely in reaction to the unsatisfactory upper limit for age at onset that prevailed for a diagnosis of schizophrenia according to DSM-III.\textsuperscript{17,26,27} However, both DSM-IV and ICD-10 have removed any reference to the age at onset of symptoms for schizophrenia or delusional disorder.\textsuperscript{7,8} Through the European or American literature, here we aim to clarify the position of late-life psychosis and, more particularly, PHC. We also give some results of a study that compared 30 female patients with PHC admitted consecutively in a psychiatric setting and 30 female patients with schizophrenia, matched for age at interview.\textsuperscript{28} We assessed all patients with a face-to-face psychiatric interview using the Diagnostic Interview for Genetic Study (DIGS)\textsuperscript{29} and the Family History—Research Diagnostic Criteria (FH-RDC)\textsuperscript{10} in order to detect presence of psychotic disorders in the relatives of both groups.

**Clinical aspects**

Patients with PHC are often described as having been reclusive, suspicious, and hostile throughout life. In France in 1911, Ballet found abnormal personality traits in 80% of patients with PHC.\textsuperscript{1} This description shares common characteristics with late paraphrenia.\textsuperscript{14,16,31} However, some patients have a good academic and employment record, even if social isolation may frequently occur.\textsuperscript{32} In a French sample of 30 patients with PHC, the majority of patients were married and had children, but half of them lived alone at the beginning of the illness.\textsuperscript{28} The vast majority of PHC patients were working or retired, in contrast to the majority of the group of patients with schizophrenia, who had a mentally handicapped status.

Age at onset of PHC in females is classically around the menopause. While the majority of cases of PHC begin after 30 years, Pull and Pichot did not base the definition of this disorder on the age at onset, in contrast with the concepts of late-onset schizophrenia and late paraphrenia.\textsuperscript{44} In our study, the mean age at onset of PHC was 50 years, ie, 20 years older than in the schizophrenic groups. In this respect, the International Late-Onset Schizophrenia Group Consensus Conference emphasized that categorization by specific age-at-onset ranges was relatively arbitrary with a proposed cutoff of 40, 45, 55, or 60 years.\textsuperscript{25}
The PHC entity was mainly based on clinical characteristics. PHC patients are more likely to have hallucinations than schizophrenic patients, particularly when multiple sensory modalities are concerned. This clinical picture shares common characteristics with late paraphrenia,14,15,33 or late-onset schizophrenia.34,35 Specific hallucinations including conversing voices, running commentary auditory hallucinations, and thought echo are characteristic of the PHC group. All these hallucinatory experiences characterized the mental automatism described by de Clérambault in 1924 for the isolation of the concept of PHC,2 and are a further important clinical difference from cases of schizophrenia. The delusions in PCH were also often well-systematized and fantastic, with paranoid and persecutory content and the presence of “partition delusions.” Persecution and ideas of reference are found in excess in the PHC group, consistent with established features of late paraphrenia or late-onset schizophrenia.35 PHC patients are also more likely than schizophrenic patients to complain about delusions of being controlled and exposed to thought insertion. These features characterized the “ideoverbal” automatism described by de Clérambault and were particularly important in the hallucinatory experiences in a variety of sensory modalities for the first isolation of the concept of PHC one century ago. The description of positive symptoms and, particularly, the kind of delusions and the modality of hallucinations all share common aspects in PHC, late paraphrenia, and late-onset schizophrenia. The description seems to be more homogeneous and more pronounced in PHC patients who have at least one kind of hallucination and always have persecutory delusions. Negative symptoms are very rare in the PHC group, while they are much more frequently cited in schizophrenia, particularly for cases with an early onset. Pearson observed that the occurrence of negative symptoms increased with duration of illness, and decreased with age at onset.44 These findings are consistent with the idea that negative or deficit symptoms are characteristic of an early-onset form of schizophrenia,36 and are not detected in PHC. PHC patients were initially described by the absence of formal thought disorder, though in 1961 Kay and Roth reported incoherence of speech, the use of neologisms, circumstantiality, or irrelevance in 30% of their patients with late paraphrenia,15 and Pearson et al found thought disorder in 6% of patients with late-onset schizophrenia.46 Formal thought disorder may not exist in PHC, though it is considered to be a core feature of schizophrenia.37,38

### Risk factors

#### Brain imaging

Computed tomography and magnetic resonance imaging studies have reported nonspecific structural changes (higher ventricle/brain ratio, third ventricle volume) in patients with late-onset psychosis compared with age-matched controls. Studies on the density of dopamine D2 receptors (positron emission tomography [PET] or single photon emission computed tomography [SPECT]) have produced discrepant results.39,40

#### Sensory deficit

Old age is often associated with reduced sensitivity and acuity of taste, smell, touch, vision, and hearing. Although both auditory (particularly long-standing conductive deafness) and visual deficits have been related to the development of paranoid features in old age,41 this observation may be explained by the reluctance of these patients to seek corrective measures. However, reports of a significant reduction in psychotic activity after a hearing aid has been fitted indicate that deafness is, at least in part, a predisposing factor for the development of symptoms, even though it is difficult to explain such a complex disorder on the basis of a simple sensory deficit.42

#### Gender and hormonal status

Practically all studies of late-onset schizophrenia and late paraphrenia, or more particularly PHC, report a large excess of affected women. Reported female/male ratios range from 6:143 to 45:244; in one PHC group, Bénazet found a 1:7 female/male ratio.45 Seeman and Lang proposed that the higher level of estrogen before the menopause might result in the delayed onset of symptoms in women.46 Pearlson et al reported an increased density of D2 receptors in late-onset schizophrenia,39 although a recent attempt to replicate this finding has failed.47 Estrogens seem to modulate the sensitivity of D2 receptors in brain and, according to some authors, estrogens could have a neuroleptic-like effect.48 Moreover, estrogens can reduce the dopamine concentration in the striatum,49 thereby modulating the sensitivity and the number of dopamine receptors.50,52 Estrogens could thus act as a protective factor, delaying the onset of the psychotic syndrome.
in women. The menopause could represent a high-risk period in vulnerable women in terms of loss of estrogen. An alternative hypothesis is that, rather than the existence of a delaying factor detected in all female patients, some vulnerability factors may be involved in a subgroup of patients, with a particular range of age at onset. For example, in a recent genetic analysis, we observed a significant excess of one D2 receptor gene haplotype in schizophrenic patients, specifically in a subsample of patients with a disease onset occurring after 20 years of age.53

Another hypothesis is that significant vulnerability genes are differentially expressed among generations, with a milder form and late onset (such as PHC) in older generations, and a more severe disorder with younger age at onset (such as schizophrenia) in younger generations. Unstable mutations (Figure 1) can shed light on such mechanisms.54 If such mutations are involved, and if the PHC phenotype is the milder form of the schizophrenia spectrum disorder, we should observe a decreased risk in ascendants (this is the Sherman paradox), and an increased risk in descendants. This can be analyzed on the basis of our 30 families with PHC.

Family history

Family, adoption, and twin studies suggest that there are genetic factors in the risk for schizophrenia. The frequency of schizophrenia in the relative of an affected proband is close to 10%, compared with 1% in the general population.55 Unfortunately, the literature on familial risk in PHC or late-onset schizophrenia is rather sparse, partly because of the difficulty in conducting such family studies in elderly patients who often have few surviving relatives. Moreover, these studies often lack a methodological description for the identification of family members and the definition of illness, including the age at onset. Despite these limitations, the risk of schizophrenia in relatives of late-onset schizophrenic probands ranges from 2.3%44 to 9.8%12 for siblings and from 0.0%

![Figure 1](https://example.com/figure1.png)

Figure 1. Expanded trinucleotide repeats, or unstable DNA, are the biological basis of the clinical phenomenon of genetic anticipation in different neurodegenerative disorders, and could be involved in schizophrenia. Usually, the CAG (triplet) repeat is repeated a certain number of times, for example, <6 times (yellow bar). It remains this length for life and generation after generation. In some disorders, a mutation occurs, which is not explained by a deletion or a substitution of a nucleotide, but rather by a loss of control of the number of times a triplet is repeated. When this number is above a certain cutoff (in this case, 42), then the expansion is no longer controlled, and will continue to expand in successive generations, although the phenotype is not yet modified for subjects with moderate size expansion (orange bar). In the next generation, the mutation is longer (the coded protein could be less functional), then, when a certain number of repetitions are observed (eg, 200 in this figure), the disorder is present (red bar). In further generations, the mutation usually increases, explaining worsening severity and/or earlier age at onset with each succeeding generation and accounting for the anticipation effect at the epidemiological level.
to 4.4% for parents. Thus, it appears that the prevalence of schizophrenia in the first-degree relatives of late-onset schizophrenic probands is greater than in the general population, but lower than in the first-degree relatives of earlier-onset schizophrenic patients.

Previous studies showed a trend toward decreasing familial risk schizophrenia with increasing age at onset. Some reports have suggested the existence of a subgroup of affected females with late onset and no family history of schizophrenia. In addition, later-onset illness is associated with clinical peculiarities (intensity of delusions and presence of multiple-sense hallucinations, rarity of negative symptoms, or thought disorder) and a better outcome. Only Bleuler and Post give data on age at onset in relatives, making any definite conclusion difficult to draw.

In our sample, we found that subjects with PHC had less familial risk (6/501) compared with schizophrenic subjects (17/418) ($\chi^2=7.70$, df=1, $P=0.006$) (Table I). This difference is mainly explained by the presence of less-affected sibs in PHC patients compared with schizophrenic patients (2/83 versus 9/78; $\chi^2=5.37$, df=1, $P=0.02$) and a tendency for less-affected ascendants (none versus 5/236). There were nearly equal numbers of affected descendants (4/83 versus 3/78). Furthermore, we found that age at onset was moderately correlated within families ($\rho=0.501$, df=15, $P=0.097$), highly correlated within sibships ($\rho=0.629$, df=24, $P=0.004$), but not correlated throughout different generations within families ($\rho=0.389$, df=16, $P=0.22$).

Subjects with PHC thus had less family history of schizophrenia than the schizophrenic patients in our sample, but were associated with an increased risk of an earlier and more severe psychotic phenotype (ie, schizophrenia) in descendants, without any detected case of PHC in the relatives of the proband. This is compatible with the anticipation effect, which has already been suggested for schizophrenia by many studies.

Anticipation describes an inheritance pattern within a pedigree where disease severity increases or age at onset decreases in successive generations. This phenomenon has been described in nearly 20 neuropsychiatric disorders such as fragile X syndrome and Huntington’s disease. In these disorders, anticipation has recently been shown to correlate with the expansion of trinucleotide repeat sequences at the disease locus (Figure 1). These diseases represent a class of disorders caused by unstable DNA sequences that can change in each generation, accounting for anticipation. The discovery in rapid succession of several diseases caused by expansion of triplets raises the possibility that additional neuropsychiatric disorders with clinical features of anticipation could be candidates. The common properties of these mutations are the departures from mendelian inheritance and the highly variable phenotype with wide-ranging age at onset, which are well-known characteristics of schizophrenia. More direct analyses of the genome have been made in order to detect large expansion of triplets in severe and early forms of schizophrenia, with conflicting and, above all, negative results. The complexity of the methods required to detect a specific unstable mutation, and the clinical and genetic heterogeneity of schizophrenia, probably explain the presence of many negative studies and nonreplications of initially positive associations. On the other hand, epidemiological evidence in favor of anticipation can be considered as very good, because it is based on many different samples and with numerous different methodological strategies. Nevertheless, the relationship between epidemiological anticipation and unstable genes remains to be proven in schizophrenia. Evidence for the anticipation effect is reinforced by the presence of a correlation for age at onset within sibships in our sample, with a younger age at onset in recent generations. If the PHC syndrome is considered as a moderate form of schizophrenia (with moderate negative
features and late age at onset), then it could be associated with a low number of triplet repeats (but above the normal range). The absence of affected ascendants and the 2.4% frequency of affected descendants are in accordance with this hypothesis.

**Conclusion**

Clinical, epidemiological, and possibly etiopathogenic factors may thus distinguish PHC from schizophrenia. The diagnosis of PHC is mainly classified under schizophrenic disorders (paranoid type) according to DSM-IV. hampering the retrieval of these cases. According to DSM-IV, schizophrenia appears to be fundamentally heterogeneous and presumably consists of a group of related disorders. While cases of schizophrenia with onset after age 45 are mentioned, in the same way as early-onset cases, they are associated with a higher proportion of women, better occupational and marital histories, more paranoid delusions and hallucinations, and less disorganization and negative symptoms. PHC might represent a more homogeneous entity with precise clinical characteristics. The clinical, epidemiological, and possibly etiopathogenic specificities of PHC cannot be helpful in delimiting the “schizophrenia spectrum” if PHC is classified under the “schizophrenia” category, following the DSM-IV. In order to check the importance and specificities of PHC, a subcategory for odd delusional disorders (or even a specific category) could be useful, not only for its clinical value, which was considered as obvious in France nearly a century ago, but also for the important problem of the phenotype boundaries in schizophrenia, for example, in genetic analyses. The data provided herein may illustrate the fact that taking into consideration the PHC phenotype could shed light on the clinical approach to the concept of anticipation in schizophrenia.

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El concepto francés de “psicose hallucinatoire chronique”, ¿una forma preliminar de esquizofrenia?

La distinción entre la esquizofrenia y los síndromes delirantes crónicos (que incluyen el concepto francés de “psicose hallucinatoire chronique” (PHC) o psicosis alucinatoria crónica, la parafrenia y la parafrenia tardía) se utiliza actualmente en varios países europeos, a pesar de que no existen criterios internacionales para los delirios crónicos y bizarros. El concepto francés de PHC está caracterizado por una psicosis de aparición tardía, predominantemente en mujeres, con alucinaciones intensas y frecuentes, pero casi sin características dissociativas o síntomas negativos. La PHC y la esquizofrenia de aparición tardía pueden tener factores de riesgo en común, los cuales pueden ayudar a diferenciar estos trastornos de la esquizofrenia de aparición en la juventud, especialmente en relación con el potencial papel de: (1) la hipótesis del estradiol, (2) el impacto del déficit sensorial, (3) las posibles alteraciones cerebrales específicas o (4) las mutaciones genéticas específicas. De acuerdo a esta hipótesis, y teniendo en cuenta el análisis de la agregación familiar de la PHC, nosotros evaluamos acá la posibilidad que la PHC represente una forma menos severa de esquizofrenia, lo que podría explicar en parte la “paradoja de Sherman”, que también se observa en la esquizofrenia. La paradoja de Sherman describe el hecho que familias con transmisión de multiplex frecuentemente tienen sólo un ascendiente afectado, lo que significa que un caso esporádico aislado constituye el origen de una familia con una alta carga genética. Por esta razón es que nosotros proponemos que si las mutaciones instables están involucradas en el riesgo de esquizofrenia, entonces la PHC podría representar un trastorno moderado que pertenezca al fenotipo del espectro de la esquizofrenia.

Le concept français de psychose hallucinatoire chronique - forme préliminaire de schizophrénie ?

La distinction entre la schizophrénie et les syndromes de délire chronique (comprénant la psychose hallucinatoire chronique [PHC] – concept français – la paraphrénie et la paraphrénie tardive) est couramment utilisée dans divers pays européens, bien qu’il n’existe pas de critères internationaux concernant les délires chroniques et bizarres. Le concept français de PHC est caractérisé par une psychose d’apparition tardive, principalement féminine, accompagnée d’hallucinations riches et fréquentes, mais presque sans manifestation dissociative ni symptôme négatif. La PHC et la schizophrénie d’apparition tardive peuvent avoir des facteurs de risque communs, pouvant aider à les différencier des schizophrénies d’apparition précoce, particulièrement en ce qui concerne le rôle potentiel : (1) de l’hypothèse estrogénique ; (2) de l’impact du déficit sensoriel ; (3) d’éventuelles anomalies cérébrales spécifiques ; ou (4) de mutations génétiques spécifiques. Partant de cette hypothèse, et tenant compte des analyses d’agrégation familiale de la PHC, nous discutons ici la possibilité que la PHC constitue une forme moins sévère de schizophrénie, ce qui expliquerait en partie le « paradoxe de Sherman » observé également dans la schizophrénie. Ce paradoxe se réfère à des familles multiplexes dans lesquelles il n’y a souvent qu’un seul ascendant atteint, ce qui signifie qu’un cas isolé sporadique est à l’origine d’une famille avec un lourd fardeau génétique. Nous proposons donc, dans le cas où des mutations instables seraient impliquées dans le risque de schizophrénie, que la PHC représente un trouble mineur faisant partie du phénotype du spectre de la schizophrénie.

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