Diagnostic and therapeutical challenges of "late-onset" psychosis.

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Abstract

We present a case report that fits on the concept of "paraphrenia" described as a chronic psychotic disorder in old age, in order to review the following teaching points: 1) Differential diagnosis to consider in "late-onset" psychosis include: Delirium; Drugs; Disease; Dementia; Depression or other affective disorders; and Delusional disorder or schizophrenia spectrum disorders; 2) "Late-onset" Psychosis have different clinical features whose specificity is not considered on current international diagnostic classification criteria; 3) Organic factors might play a significant role on "late-onset" psychosis, and diagnosis of cognitive impairment or dementia has to be considered; 4) The use of antipsychotics in old people has to be more cautious, and they show more problems of adherence to treatment than the general population; 5) Cognitive and social factors might overlap and contribute to a decrease of capacity on decision making in these patients.

Keywords: Late-onset psychosis, Late-paraphrenia, Dementia, Capacity.

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Introduction

Old population is growing larger and the number of cases of "late-onset" psychosis seems on the increase. These forms of psychosis have different clinical features, whose specificity are not considered on current international diagnostic classification criteria and may respond different to treatment. Whether this is due to pathoplastic effects, organic factors or social expectations remain speculative [1].

We present a "late-onset" psychosis case report that fits on the concept of "late-paraphrenia" described firstly by Pelliza and Bonazzi in 1955: a chronic psychotic disorder of old age, characterized by a hallucinatory-paranoid state which seemed to appear more frequently in females with sensorial deficits and social isolation [2].

The goal of this work is to review, through this case report, the differential diagnosis of late-onset psychosis, the concept of "late-paraphrenia", the influence of organic brain changes and social factors on late-onset psychosis, and some important considerations for its treatment. It is also worthy to remark the negative influence on capacity of all these factors.

Case Report

Mrs. Carmen (C) (fictitious name) is an 81 years old lady, with history of chronic depressive disorder (dysthymia) since her twenties, and vulnerable personality traits (dependency, insecurity). She has primary studies and has been a housewife all along her life. She lives alone, her husband passed away 20 years ago and she has complained about loneliness and lack of support from her sons since then.

Medical records show history of hypertension, dyslipemia, osteoporosis, chronic renal disease (CRD), and unspecific neurological symptoms such as tremor, rigidity and myoclonus in upper limbs and cervico-facial dystonia in the last 5 years. She also has impaired vision and audition because senility. She is on treatment with one anti-hypertensive, a statine, omeprazol, calcium, escitalopram 10 mg/d (prescribed in our Mental Health Unit years ago), clonacepan 0.50 mg/d (prescribed by neurologist because neurological symptoms) and quetiapine 25 mg/d (prescribed by neurologist 1 year ago because psychiatric symptoms.

She is referred to our MHU due to behavioral disturbances in order to assess capacity, because different social services and financial entities have alerted her sons of an aggressive behavior against them. Mrs. C rejects to come to our first programmed visit. Her sons told us that, in the last 2 years, she is obsessed with money, and that she has progressively developed suspiciousness against them, as well as against social services, which have difficulty to provide her domiciliary support because of that. She was referred to the Neurologist one year ago because of these symptoms, with suspicion of an incipient dementia, but she has discontinued her follow-up after confrontation of need of supervision.

In this critical situation, we contact with Mrs. C's Primary Care Doctor to try to get her collaboration and allow our intervention. As she has been previously attended on our MHU for years, and she is on treatment with psychiatric drugs, finally she accepted to attend to our MHU for prescription review.

Mr. C. explained to us that she had interrupted follow-

up in our MHU because an adverse drug reaction to a prescribed medication (probably an antidepressant, but she did not remember the name of the drug). She shows a cared hygiene and appearance and a good rapport and empathy with us during interviews. Since the first meeting, she comes always on the right time and date to the programmed visits by herself. She is in good mood, but she feels worried, anxious and embarrassed about her troubles with her sons and "the social assistant", who she say "to have rewritten or stolen all important documents in her house" and "to have stolen her savings by theft of her identity". Spontaneous speech tends to persevere on these paranoid delusional thoughts, and it is circumstantial, but coherent. She apparently has not troubles of perception, but she thinks that "somebody, eventually the social assistant, is continuously keeping surveillance on her inside her flat…and even outwards, when she travels away", "the social assistant is able to enter to her flat by an unknown mechanism, possibly through the closed door or the antenna of the house". She has not insight of illness or disability.

On cognitive evaluation (Exploración Neuropsicológica Mínima en demencias, ENM.dem, Pablo Duque) results were as follows: she is well oriented in time and space; she shows a significant impairment on immediate recall (4/24), which noticeably improves up to normal scores with semantic cue (20/24), despite some intrusive phenomena (3); delay recall was also impaired (0/12) and partially improved with cues (9/12); she shows a low verbal fluency (6-7 words/min); and impaired constructive praxis (Clock-Drawing Test (CDT) 2/10); performance on ideo-motor praxis, nomination and visuo-spacial abilities (overlapping images, CDT-copy) was preserved; abstraction score was border-line (4.5/6).

She is relatively independent for Instrumental Daily Living Activities (DLA), except for financial matters (Lawton 8/8).

Analysis of blood only showed a known moderate CRD (Glomerular Filtration Rate 56.5 ml/min) and mild anemia (hemoglobin 11.6 mg/dl). Vitamin B12, Folate and iron metabolism were normal. Thyroid function test was normal. Urinalysis was not pathological. Brain TC and MRI showed: periventricular white matter changes, chronic micro-vascular ischemic changes and cortico-subcortical atrophy. Brain SPECT showed: hypoperfusion on basal ganglia and right thalamus. EEG showed inespecific slow wave discharges.

Our diagnosis is: delusional disorder (F22.0 ICD-10) and Mild Cognitive Impairment (MCI) (F06.7 ICD-10). But diagnosis of incipient dementia should be considered on evolution.

Our therapeutic goals are: 1) to achieve a therapeutic bound with patient that allows intervention, 2) to offer a therapeutic milieu to validate emotions and to reformulate patient inquiries, 3) slow titration of antipsychotics according tolerance and response, 4) to evaluate, in coordination with neurologist, indication for prescription of anti-dementia drugs, 5) to elaborate, in coordination with social services, an acceptable strategy to provide social support to the patient, 6) to inform legal institutions, with the knowledge of the patient, in order to consider legal protective measures.

Discussion

Accurate diagnosis of psychosis in older populations is essential, as its treatment varies depending on the context in which it appears. Although identifying the cause of psychosis in older patients can be challenging, the unique clinical features associated with the different disorders can help in diagnosis [3].

A useful way to think about the differential diagnosis of psychotic disorders is to use the "six **D**'s approach" that distinguishes disorders based on the timeline of their presentation [4]:

a) Secondary psychoses (acute or sub-acute course)

- Delirium (days to weeks)
- Drugs, alcohol, toxins (days to months)
- Disease (days to months)

b) Primary psychoses (sub-acute or chronic course)

- Depression and other affective disorders
- Dementia
- Delusional disorder and schizophrenia-spectrum disorders

Approximately 60% of older patients with newly incident psychosis have a secondary psychosis. Clinical presentations that should raise suspicion of secondary causes of psychosis include: absence of family or personal history of mental illness, unusual age of onset and characteristics of presenting psychiatric symptoms, limited response to psychiatric treatment, psychopathology develops following an abrupt personality change, comorbid medical condition or use/ withdraw of drugs with known association with mental illness, abnormalities of cognition (particularly memory or consciousness) [4], accompanying disorientation/confusion and visual hallucinations [3].

Our patient presented psychotic symptoms for the first time when she was 79-80 and she shows signs of memory impairment. However, psychotic symptoms in our patient show a chronic course (1-2 years), she is on a relatively good health at her age and we did not find any medical cause related with her psychotic symptoms in laboratory workup, neuroimaging nor EEG. So that, following the elimination of secondary causes, a primary psychotic disorder should be considered.

In the context of past psychiatric history of our patient, a diagnosis of major depressive disorder should be considered. Older persons with major depressive disorder are more likely to have psychotic features, being delusions the most common [4]. However, Mr. C shows a good mood and emotional reactivity in interviews, she presents very mild affective

symptoms and secondary to her experience of delusions, and her delusions would be incongruent with a depressive mood.

For diagnosis of dementia or major neurocognitive disorder deficits in at least one of the following must be present: complex attention, executive function, learning and memory, language, perceptual motor or social cognition [4]. Mr. C shows impairment in some memory task (recall) and tasks sensitive to executive dysfunction (verbal fluency, CDT). Moreover, some of her psychotic symptoms might be due to misinterpretation because cognitive failures. But diagnosis of dementia requires cognitive deficits to interfere with capacity for independence in DLA. Our patient shows impairment on financial issues, apparently more related at this moment with her psychotic beliefs than with her cognitive deficits, but she keeps independency in all other instrumental DLA (including purchases, cooking, management of prescriptions, and routine national trips). So that, for the moment, we diagnosed MCI or minor neurocognitive disorder. Psychotic symptoms are rare in MCI patients. However, presence of these symptoms may reflect a major risk of developing dementia [5].

Despite other cognitive domains can be impaired, an impairment episodic memory is seen most commonly in MCI patients who subsequently progress to a diagnosis of Alzheimer Dementia (AD) [6]. Our patient has impairment on memory recall, but recognition memory is much better, suggesting impaired retrieval mechanism, typical of subcortical forms of cognitive impairment such as in Lewy Body Dementia (LBD) [7].

Moreover, to meet the core clinical criteria for MCI due to AD it is necessary to rule out other systemic or brain diseases that could account for the decline in cognition: (1) Parkinsonism, prominent visual hallucinations, fluctuation on cognition, a non-amnestic cognitive profile, deficits on visuo-spatial task such as draw copy, rapid eye movement sleep abnormalities, and slowing on EEG, often seen in LBD [6,7]; (2) multiple vascular risk factors and/or the presence of extensive cerebrovascular disease on structural brain images, which is suggestive of vascular cognitive impairment, (3) prominent behavioral or language disorders early in the course of disease that may reflect fronto-temporal lobar degeneration (FTD), or (4) very rapid cognitive decline that occurs over weeks or months, typically indicative of prion disease, neoplasm, or metabolic disorders [6].

Our patient has some vascular risk factors (dyslipemia, hypertension) and brain images show white matter lesions and a generalized (cortico-subcortical) atrophy. White matter lesions in the context of people aged over 75 years often indicate subcortical vascular disease; and prospective studies show that white matter lesions and signs of atrophy are strong predictors of dementia. In contrast with international standardized diagnostic criteria for diagnosis of vascular dementia (VaD), based in large multi-infarct disease, there are many studies that showed that subcortical vascular disease (also known as Binswanger's disease) was the main cause for most cases of VaD [8].

Psychotic manifestations (hallucinations, delusions) can present in virtually every type of dementia [9], but they are rare in FTD (about 2.3%) [10]. In dementia, delusions tend not to be bizarre or complex, most commonly manifest as either misidentification or paranoid delusions [3]. Prevalence of psychotic symptoms in demented patients is low-moderate (generally bellow 30%) compared to other behavioral and psychological symptoms of dementia (BPSD). Psychotic symptoms in dementia are generally associated with greater cognitive impairment [11], but in VaD the severity of cognitive impairment does not appear to be associated with the presence or severity of psychosis [3]. Some authors found that severity of the paranoid and delusional ideation in AD patients was significantly associated not with test of general cognition (Mini-Mental Status Examination (MMSE)) but with test sensitive to executive dysfunction (CDT [12], verbal fluency test [13]). Subcortical vascular pathology usually interrupts fronto-striatal circuits, prevailing attention deficits, information processing and executive function failure [8]. This could have been a factor for development of psychosis in our patient, but giving that our patient does not accomplish criteria for diagnosis of dementia jet, we had to consider other forms of primary psychotic disorder, remaining a delusional or schizophrenic spectrum disorder.

Schizophrenia with onset after 60 years is named "Very-late schizophrenia" by international consensus [9]. While early reports suggested that individuals with early-onset schizophrenia (EOS) and late-onset schizophrenia (LOS) exhibit similar levels of global psychopathology, numerous studies have identified differential clinical features. For instance, individuals with LOS more often exhibit visual, olfactory and tactile hallucinations, and when auditory hallucinations are present, they tend to be of an accusatory nature or involve a third-person running commentary. Additionally, they are more likely to experience persecutory and partition delusions (the belief that people can pass through what would normally constitute a barrier to such passage), and less likely to have a formal thought disorder or severe negative symptoms [3].

The term "Paraphrenia" was proposed to define a group of chronic psychosis characterized by a vivid and systematized delusional system (with or without hallucinations), but unlike schizophrenia, without disturbances of emotion and volition. Later, Pelliza and Bonazzi proposed the term "late-paraphrenia" to differentiate presentation of this clinical picture in old age [2]. This term is not specifically included in the current international standardized diagnostic criteria; for example, in ICD-10 "late-paraphrenia" is included under the diagnostic category "Delusional Disorders" (F22.0 ICD-10). Delusional disorders are more often seen in older patients and are not an uncommon cause of psychosis in this population [9]. However, several authors suggest that a valid and reliable diagnosis in psychiatry should go beyond the simple classification of symptoms, and that the concept of "paraphrenia" has not lost its usefulness [2]. A number of key factors (all of them present in our patient) have been related

to this particular condition such as ageing, preponderance of women over men, hearing impairment, social isolation, maladaptive personality [14] and organic brain disease [15].

Numerous studies have pointed out that "late-onset" psychotic symptoms are often associated with organic brain damage, in view of the fact that neuroimaging studies show lesions qualitatively and quantitatively different from those observed in EOS [15,16]. Moreover, a controlled study assessing cognitive profile of patients clinically diagnosed of "late-paraphrenia" showed that patients performed significantly worse on measures of general cognitive ability and executive functioning than controls [16]. As we have discussed before, our patient shows signs of brain damage and she shows impairment on task sensitive to executive dysfunction.

Deterioration of cognitive functions occurs very slowly in "late-paraphrenia" patients but may lead to mild dementia over a period of years, some authors report an incidence of 20-37% in their series of patients. Some researchers have found the presence of neurofibrillary tangles (NFT), primarily within the entorhinal cortex, in these patients, but amyloid deposition remained scant. They suggest that clinical and neuropathology features of "late-paraphrenia" are similar to those described for NFT-predominant senile dementia. Overall, data suggest that "late-onset" psychosis in general may constitute a prodromal stage of dementia. This is also in keeping with the finding that patients with mild cognitive impairment (MCI), including those of non-amnestic types, have a higher risk of converting to dementia than the general population [14].

Not only diagnosis, but also treatment of late-onset psychosis is a challenge. The use of antipsychotics in older adults can be difficult due to the various, and often serious, side effects associated with such medications in this population [3]. Some evidence supports the use of atypical antipsychotics, mainly because of the propensity of first-generation neuroleptics to induce extrapyramidal symptoms and tardive dyskinesia, to which older individuals are more prone. However, both classes of antipsychotics have been implicated in increasing cardiovascular and all-cause mortality. According to a survey of expert clinicians in the US, risperidone should be the drug of choice in LOS and quetiapine, olanzapine and aripiprazole are good second-line options [9]. Risperidone and olanzapine are also some of the most commonly used antipsychotics in treating delusional disorder and, although results are variable, some evidence supports their efficacy [3]. The International Consensus suggest that 25 to 50% the doses of that used in younger patients could be used in LOS patients, with a very low initiation dosage, and a cautious increments up to the lowest effective dose.

No study has assessed treatment adherence in patients with LOS specifically, but both psychosis and ageing have been linked to adherence problems. Partial adherence to treatment is observed in at least 20–50% of patients in the general population, but these rates approach 70-80% in persons with psychotic disorders. Several factors related to old age may result in poor adherence, including sensory impairments, cognitive deficits, osteoarthritis, restricted mobility, lack of transportation, social isolation, financial insecurity, polypharmacy, and increased sensitivity to side effects. Many of these factors are present in our patient, and we are having problems in finding a well tolerated antipsychotic at an appropriate dose. Depot medications are an alternative in non-adherent patients diagnosed with a chronic psychotic disorder, minimizing the plasma level fluctuations that can be especially problematic in older people [9].

Due to the cognitive impairment showed by our patient and all the previously commented factors that could increase the risk for developing dementia, we have to consider the potential benefit of anti-dementia drugs on diminishing risk or delaying dementia. Most controlled studies have shown a small but significant benefit of cholinesterase inhibitors on cognition in VaD, but the magnitude of this effect has been slight (roughly half the improvement seen in the AD's studies) and benefits on global functioning, activities of daily living and behavior have not been consistently reported. Combined with concerns over diagnostic validity and possible side-effects, this small effect has led both regulatory bodies and guideline groups to conclude that cholinesterase inhibitors and memantine should not be used in patients with VaD [8].

It is also critical to assess capacity for healthcare and financial decisions, that in the case of Mrs. C it was the reason for referral to our MHU. Clinicians have to protect patients by early detection of the factors that diminish their capacity. To evaluate capacity in decision making we should contemplate not only changes in neural circuits and cognitive functions, but also the importance of social factors. At the cognitive level, impairment of executive functions (flexibility, inhibition, working and procedural memory, ability to plan the future) and episodic memory have been associated with a deterioration of financial decision-making capacity [17]. In our particular case, not only cognitive features, but also the apprehension that our patient has of her social environment are decreasing her ability to manage financial issues.

Conclusion

Our revision suggests that psychotic states arising in late life are associated to brain injury or dysfunction. There is strong evidence that psychotic symptoms may be the expression of faulty neuronal systems located in the frontal lobes. Subcortical vascular disease is more frequent than other forms of cerebro-vascular disease and usually interrupts fronto-striatal circuits, causing attention deficits, information processing and executive function failure. "Late-onset" psychosis is frequently associated with some degree of cognitive impairment and it also affects social adjustment, compromising capacity in decision making of the patients. Diagnosis and treatment of these cases is frequently a challenge. Future research should rely on the identification of specific psychopathological features to formulate more

specific diagnosis in "late-onset" psychosis, as well as their associated risk factors; in order to prevent and facilitate a more specific treatment for these conditions.

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