PSILOGOS

Caso Clínico / *Case Report*

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Schizophrenic-like psychosis presentation of Huntington's disease: on diagnostic features, therapeutic implications, and Future Directions. A case report.

Psicose esquizomorfa como apresentação de doença de Huntington: sobre aspectos diagnósticos, implicações terapêuticas e direcções futuras. Um relato de caso.

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ABSTRACT

Background: Huntington's disease (HD) is the commonest monogenic neurodegenerative disorder. Behavioral and psychological disturbances may predate the onset of motor and cognitive symptoms. Psychotic features are depicted by a minority of patients, usually as atypical psychosis.

Aims: To report and discuss a clinical case with significant particularities, from anamnesis and diagnosis to treatment considerations.

Methods: Direct clinical interviews and electronic clinical process examination. Research on MEDLINE database, using the MeSH terms: Huntington, psychosis, schizophrenia.

Results and Conclusions: A 63 year old male presented an overall course and phenomenology suggestive of very late onset schizophrenia. Later investigation asserted the diagnosis of HD. We discuss the clinical features, pharmacological management and the obstacles to consider when obtaining a family history, while highlighting the importance of understanding microsocial particularities when valuing social and occupational functioning. The association between HD and psychotic features may prove relevant to further understand the genetic correlates of schizophrenia.

Key-Words: Huntington's Disease; Schizophrenia; Psychotic Disorders

RESUMO

***Introdução**: A doença de Huntington (HD) é a doença neurodegenerativa monogenética mais comum. Alterações comportamentais e psicológicas podem anteceder os sintomas motores e cognitivos. Fenómenos psicóticos atípicos podem ser apresentados por uma minoria de doentes.*

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***Objectivos**: Apresentação e discussão de um caso clínico com particularidades significativas, desde a anamnese e diagnóstico até considerações terapêuticas.*

***Métodos**: Entrevistas clínicas directas e consulta do processo clínico electrónico. Pesquisa na base de dados MEDLINE, para os termos MeSH: Huntington, psicose, esquizofrenia.*

***Resultados e Conclusões**: Um homem de 63 anos apresentou um curso e fenomenologia sugestivos de esquizofrenia de início tardio. A prossecução do estudo firmou o diagnóstico de HD. Discutem-se os aspectos clínicos, a orientação terapêutica, e os obstáculos a considerar na obtenção dos antecedentes familiares, sublinhando a importância de particularidades micros-sociais na valorização da funcionalidade socio-ocupacional. A associação entre HD e fenómenos psicóticos poderá relevar na compreensão dos correlatos genéticos da esquizofrenia.*

***Palavras-Chave:** Doença de Huntington; Esquizofrenia; Perturbações Psicóticas*

INTRODUCTION

Huntington's disease (HD) is the most common monogenic neurodegenerative disease and the commonest form of genetic dementia, with a prevalence of 10.6-13.7 individuals per 100 000 in the Western world. The transmission is autosomal dominant, meaning that the presence of the mutation on either allele will lead to the disease. The mutation consists of an expanded CAG triplet near the Huntingtin gene (HTT), which translates into the presence of a polyglutamine expansion at the N-terminus of the Huntingtin protein[1]. Neuropathology studies demonstrate massive striatal degeneration, with a loss of up to 95% of the GABAergic medium spiny neurons projecting to the globus pallidus and substantia nigra. Cortical and subcortical atrophy is also visible. Etiopathogenic studies are focusing on early synaptic dysfunction, which point to a dysregulation of glutamate release in the striatum mediated by N-metil D-aspartate (NMDA) receptor, followed by cellular death and progressive disconnection between cortex and striatum. Current studies suggest that HD treatments need to be designed according to the stage of disease progression[2]. Disease onset is clinically established when unequivocal extrapyramidal motor signs are displayed, with a typical midlife onset (average 45 years old). Patients often experience psychiatric and cognitive symptoms alongside subtle motor disturbances for many years before HD diagnosis is established, what some authors have called a "prodromal" phase of HD[3]. The disorder is further complicated by its notorious clinical heterogeneity, even within families, regarding the relative weight of the motor, cognitive and psychiatric features. Chorea is the most striking motor manifestation, ranging from short-lived, occasional and semi-purposeful excessive movements or twitches of the face and extremities in earlier stages, and progressing to constant and ample movements of the entire body impairing eating, balance and voluntary movement in general. Cognitive symptoms are universal in HD, also ranging from mild cognitive impairments in earlier stages, progressing to overt subcortical and frontal dementia.

A wide array of psychiatric manifestations has been described, with depression and anxiety being by far the most common. Apathy, irritability and aggression, obsessive-compulsive features, sexuality disturbances have all been associated with HD, alongside psychosis to a lesser extent[4]. Studies have identified rates of psychosis between 7-11%, with a tendency to present as isolated or atypical psychotic features, with a wax and wane course, rather than a full-blown schizophreniform expression. Although psychotic features are not clearly associated with the rate of progression of the disorder, it seems that patients with an early age of onset of HD are at greater risk of developing psychotic features. This is considered an understudied area[5]. In this report, we are particularly interested in the relation between HD and schizophrenia-like psychotic features, adding to a few other case reports that assert similar presentations, in line with the suggestion that the association may prove relevant to our understanding of the highly complex genetic correlates of schizophrenia. Additionality, we will discuss the clinical features and pharmacological management, focusing on the description of the subtle signs that pointed towards the diagnosis of HD and the obstacles to consider when obtaining a family history, while highlighting the importance of understanding microsocial particularities when valuing social and occupational functioning.

OBJECTIVES

To report and discuss a clinical case with many significant particularities (from anamnesis and diagnosis to treatment considerations), added by a short narrative.

MATHERIAL AND METHODS

The clinical elements reported were obtained through direct clinical interviews and electronic clinical process examination. The authors also performed a research on MEDLINE database, using the MeSH terms: Huntington, psychosis, schizophrenia.

RESULTS

J., a 63 year old male, was presented to the Psychiatric Emergency Department by police officers in the context of severe behavioral disturbances including physical aggression of a few unrelated passers-by and disorganized speech. The clinical records of the emergency psychiatric evaluation describe a highly systematized persecutory delusion involving the mayor of his city, and probable auditory verbal hallucinations and thought insertion phenomena. The records are scarce, seemingly because further subtler characterization was difficult as the patient proved uncooperative and hostile. Analytical examination was unremarkable. Alcohol test and drugs of abuse in the urine were negative. CT scan showed ventriculomegaly and a notable enlargement of the Sylvian fissures, reported as overall suggesting a pattern of disproportionately enlarged subarachnoid space hydrocephalus (DESH). The first few days in the ward were marked by frank hostility and a sedimented, behaviorally dynamic paranoid delusion, difficult to manage considering the noticeable sensitivity to extrapyramidal side effects of antipsychotic medication. Due to government-imposed restrictions related to the SARS-CoV2 pandemic, family visits and in-person family interviews were restricted. In our first contact with the patients' ex-wife

(signaled in the emergency report as the closest family member of the patient), it was revealed that there was a history of psychotic symptoms evolving at least three years before admission. The ex-wife (who was still living with the patient), explained that J. was illiterate, and worked as a fisherman all his life until three years, when growing conflicts with his coworkers led him to be fired. He isolated himself progressively at home, constantly mumbling about "the mayor's conspiracy against him". When he would go outside, he would "insult everyone and get into fights, even with neighbors we have known since a very young age". There had been no previous legal charges, "everyone in the villa knew him and his manias". She denied functional decline, and further explained that they were still living as a couple, and that the divorce was imposed by the patient as a "veneer to escape the control of the mayor". They had been living in that small fishing community their whole life. J. was the youngest of five, three of which were deceased due to a "family illness that came from their late mother". After relative behavioral stabilization was achieved, a neurological examination revealed subtle motor disturbances. These included grimacing, widened palpebral fissures associated with frontalis contractions, head nodding and turning, and sudden truncal movements. A neuropsychological evaluation revealed pathologic results in all areas evaluated, with an overall score in the Mini Mental State Examination of 9/30, and an Addenbrooke Cognitive Examination-Revised score of 32/100. The CT-scan images were rediscussed with a specialized neurological imagiologist, who asserted that the observed pattern was compatible with a pattern of atrophy. When we were finally able to reach the patient's son, he informed us of the diagnosis of HD in several members of the family; it became clear that this was a taboo topic, since the patient's son, an educated 40 year old man, had previously refused testing and was about to be a father. A confirmatory genetic test was performed to our patient, asserting the diagnosis of HD. A combination of Haloperidol, Olanzapine and Lorazepam were the first treatment options, with daily doses of 5 mg, 10 mg and 2.5 mg, respectively. However, due to the patients' lack of response to the antipsychotics in this treatment and the presence of extrapyramidal symptoms even after beginning Trihexyphenidyl 2mg, the initial olanzapine was discontinued and a switch from haloperidol to risperidone was tried, firstly 3mg/day with increasing daily doses until a maximum of 6 mg/day. Despite decreasing chorea and some of the behavioral symptoms such as angry outbursts, the psychotic activity was still present with this treatment option. Risperidone was then switched to extended-release Quetiapine 100 mg. Quetiapine was slowly titrated until a maximum of 300 mg and concomitantly Memantine 20 mg was added. As so, after 6 weeks and considering the many psychopharmacological trials and errors above mentioned, the patient was discharged with no residual psychotic activity, prescribed with extended-release Quetiapine 300mg, Trihexyphenidyl 2 mg bid, Memantine 20mg id and Lorazepam 2.5 mg.

DISCUSSION AND CONCLUSIONS

Our discussion will firstly focus on the practical, clinical and therapeutic issues that arose

from the case presented. Secondly, we will avow the value of schizophrenia-like psychotic presentations of HD in the understanding of the genetic basis of said non-organic psychosis, such as schizophrenia. Schizophrenia is generally regarded as an illness with onset in late adolescence or early adult life, however a minority of patients first become ill in middle or old age[6]. These late-onset cases constitute 15% of the schizophrenia patients and the literature states that approximately 20% to 25% of patients with schizophrenia have an onset of the disorder after age 40[7]. About 50% of the patients with late-onset schizophrenia have symptoms that are indistinguishable from those seen in schizophrenic patients with the more typical younger age of onset. Despite the similarities, there is no evidence that a progressive dementing disorder is associated with onset in middle or old age[6]. When the disorder arises between ages 40 and 60, it has been thought to resemble the early-onset subtype, although there are modest differences, such as a preponderance of women, a lower level of symptom severity, and less executive dysfunction. The very-late-onset subtype is also distinguished by higher rates of visual, tactile, olfactory hallucinations and a greater prevalence of persecutory, partition delusions and absence of formal thought disorder or negative symptoms as well as lower genetic load[7]. The clinical presentation of our patient could easily be ascribed to a diagnosis of very late onset schizophrenia. Both the clinical features - including systematized persecutory delusions, auditory hallucinations and thought insertion (a *Schneiderian* first rank symptom), alongside less severe negative symptoms, and the social history (good prior occupational functioning and marital history), would support this diagnosis[6]. The subtle motor signs could be easily overlooked by unexperienced psychiatrists. The long duration of untreated psychosis is also noticeable, although not exceptional – it has been recognized that smaller communities tend to be more tolerant and container of even severe psychopathology than the cities[7]. The cognitive and functional decline (which became evident as soon as the positive psychotic symptoms faded and the neuropsychological tests were performed) was unrecognized by the ex-wife and the son. Literature describes that many patients and their families consider these psychiatric symptoms the most distressing aspects of HD, as they result in severe impairment and negative effect on daily functioning[8], whereas motor and cognitive dysfunction is only moderately associated by relatives to the severity of functional and behavioral decline[9]. In our case, family perceptions of impairment appeared to be due to a sub-culturally mediated masking of the decline – in this small fishing communities, it is the norm that the male, while publicly being the authoritative figure of the couple, is solely focused on his working duties, and the female partner is in charge of running all the household matters, including shopping,finance planning and management. The burden and stigma associated with a family disease such as HD is even severer in these small, highly involved communities. That might have contributed to the resistance we encountered when discussing the family history of the patient with both his ex-wife and his son. Finally, it is worth reminding the value of reviewing the

complementary exams obtained in the emergency department, and actualizing their interpretation as new clinical information is collected – a normal pressure hydrocephalus would be a highly unlikely diagnosis in the case described[10]; the integration of the family history of HD and the quantified cognitive decline helped the imagiologist in the interpretation of the brain images obtained. Considering the psychopharmacological management, a first trial of haloperidol was prescribed in order to control the psychotic manifestations of HD. The literature enhances its potential benefit in the presence of significant chorea and abnormal involuntary movements due to its high potency[11]. Olanzapine was also tried simultaneously because of its evidence in reducing both psychosis, agitation and aggression in HD[12]. Risperidone is another second-generation antipsychotic with a possible role in the treatment of motor and psychiatric symptoms of HD, given its efficacy in Choreoathetotic movements and psychotic manifestations without affecting cognitive performances[11]. However, quetiapine was the antipsychotic of choice due to its known minimal extrapyramidal side effects. Based on current evidence, quetiapine has the ability to improve behavioral and psychotic symptoms as well as agitation and irritability without worsening motor functioning[11,13,14]. On the other hand, trihexyphenidyl acts as an anticholinergic by inhibiting the efferent impulses on the parasympathetic nervous system and consequently it is used for the treatment of tremors, spasms, and poor muscle control, so it was prescribed in order to control the motor symptoms seen in our patient[15]. Additionally, considering the critical role of NMDA receptor excitotoxicity that mediates cellular dysfunction and death in the medium-sized spiny neurons of the striatum in HD, Memantine, an uncompetitive NMDA receptor antagonist, was thought to be beneficial for the cognitive problems described[16]. The case we presented manifested schizophrenia-like psychiatric manifestations years before the development of clear extrapyramidal or cognitive changes. This contrasts with the usual psychiatric manifestations of HD. As stated in the introduction, psychotic features are relatively rare, and when present usually emerge shortly or coincidentally with the onset of motor symptoms. There are a few published studies of cases or families that develop schizophreniform psychosis[17-19], raising the question that this may be a specific phenotype of HD. The favored hypothesis is that, in the families where a co-occurrence of HD and schizophreniform psychosis is observed, there is a co-occurrence of the HD gene and a pro-schizophrenia gene or group of genes[20]. The HD would act in lowering the threshold for the emergence of a schizophrenic phenotype, in families carrying other schizophrenia oligogenes. The possible aggregation of schizophreniform phenotypes in certain HD families may help clarify how these hypothetical pro-schizophrenia genes act[21]. There are only few case reports where this association is asserted, and further investigation is needed to clarify the hypothesis of a link between pro-schizophrenic poligenetic loading and the occurrence of psychotic symptoms in HD. On the other hand, an important dimension of the case is the late emergence of a schizo-

phreniform condition, with contours of cognitive deterioration, which may be linked to a specific and common gateway to both neurodegenerative dementias and primary psychiatric disorders. In fact, late-onset schizophrenia-like psychosis appears to be a primary psychiatric diagnosis that is clinically distinct from psychotic symptoms that emerge among established dementias[22]. Also, considering J.'s case and previous history of psychotic symptoms years before the first admission, he could easily fit in a schizophrenic patient with late first-contact with the psychiatric hospital system and, therefore, according to the literature, having a two to three times higher risk of subsequently getting a diagnosis of dementia[23]. Particularly, the symptomatology framework as well as the previous family history were a main factor to consider HD and succeed in the clinical investigation. In sum, psychiatric symptoms are part of the HD clinical triad that also includes abnormal movements (typically chorea) and cognitive impairment[24]. Considering the psychiatric dimension, psychotic symptoms are rarer, with few reports describing full-blown schizophrenic features antedating motor and cognitive features of the disorder. The authors presented the case of a 63 year old male with a clinical presentation suggestive of very late onset schizophrenia. The semiological findings were discussed, alongside the impact of subcultural factors in appreciating fundamental anamnestic issues. It has been suggested that the genetic study of these patients may help clarify the identification and role of pro-schizophrenic genes. More reports are needed to reinforce this clinical hypothesis and prompt further genetic studies.

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