

PHARMACOLOGIC SIDE EFFECTS AND/OR NEUROLOGIC DISORDER: CASE REPORT

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SUMMARY

The authors presented a patient with schizophrenia and with early parallel development of neurologic symptoms. At first, symptoms were manifested by extrapyramidal syndrome due to appliance of typical neuroleptics. Therefore, therapeutic approach was diverted to implementation of atypical antipsychotics. Consequently patient developed orofacial dyskinesias which progressed in unilateral choreo-athetoid movements. This followed two hospitalizations for diagnostic workup and correction of therapy. Only repeated brain MR showed moderate cortical atrophy. However, even with different therapeutic changes and approaches, we were not able to reach any significant shift neither in psychiatric nor neurologic disturbances. The resistance on pharmacologic therapy led to suspicion of parallel development of neurologic disorder in form of Huntington chorea. Still remains the question whether primary neurologic disorder provoked psychotic process or there were two separate disorders where pharmacologic intervention accelerated expansion of neurologic disorder.

Key words: schizophrenia - antipsychotics side effects - neurologic disorder

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INTRODUCTION

Antipsychotics generally have propensity for numerous side effects. Movement disturbances present most common side effects of typical antipsychotics and are shown mostly as extrapyramidal side effects (EPSE), while atypical antipsychotics have a lower potential for their expression. These side effects are parkinsonismus, dystonia, achathisia and tardive dyskinesia. Leading to the blockade of dopaminergic transmission in basal ganglia with consequent hyperactivity of post-synaptic cholinergic neurons (Folnegović-Šmalc et al. 2003, Uzun et al. 2005). Such side effects may cause difficulties in recognizing primary neurologic disease underlying the psychosis treated with antipsychotics.

Huntington's disease (HD) is dominantly inherited neurodegenerative disorder with prevalence about 1 per 10000 individuals. Clinical manifestations consist a triad of choreic movements, cognitive decline and psychiatric symptoms which usually occur in the fourth to fifth decade (mostly between 35 and 42 years), progressing to death in

15-20 years. (Watt & Sellar 1993, MacMillian et al. 1993, Quinn & Schrag 1998) Besides abnormal involuntary movement such as chorea, there are abnormalities of voluntary movement like bradykinesia, rigidity, dysphagia, dysarthria and gait disturbances as well. Cognitive decline is classified as progressive «subcortical dementia» with prominent loss of cognitive speed, flexibility and concentration (Hayden 1981). The personality changes are the most common behavioural changes, with possible depression, apathy, irritability and aggressive manifestation. Schizophrenia-like psychosis occurs with frequency of 6 to 25%, with predominantly paranoid form (Schiauwch 1994, Cummings 1995) The risk of developing psychosis is greater in the case of early onset of Huntington's disease (Rosenblatt & Leroi 2000).

Authors present a case study of a male patient in early forties who developed schizophrenia-like psychosis and was treated with various antipsychotics due to numerous, untreatable motoric manifestations which were considered as side effects. Intensive diagnostic exploration revealed Huntington's disease underlying the psychosis.

CASE REPORT

Forty years old male, forestry engineer, divorced, from family not burdened by heritance of psychiatric or neurologic disorders. His father died when 42, due to a myocardial infarction. His premorbid function was common: he accomplished faculty degree and regular military service. He had participated in war in Croatia as well. He had a job in public service and was married. First malfunctioning became obvious when he had tried to run a firm of his own which ended unsuccessful. He had started drinking and suddenly lost his job. Shortly after he was divorced and separated from his son. He was suffering more and more from apathy and started neglecting himself, reducing all social contacts as well. Finally, at age of 36, he had developed abulia, delusions and desorganisation due to psychotic episode, and in the end of 2005. psychiatric help was sought. The treatment had begun with first generation antipsychotic flufenazine. Extrapyramidal symptoms (parkinsonisms and temporary dystonia) occurred in a very short time. No therapeutic answer was accomplished, therefore olanzapine was recommended. In upcoming months cognitive desorganisation and athymochormia persisted and very gradually dyskinesia, mostly orofacial, became obvious. Another therapy change followed: ziprasidone accompanied by side effect - sedation. We have tried again with olanzapine, but in lower doses. Few months passed with therapeutic effect considering very discrete cognitive and affective improvement, and slightly reduced dyskinesia. Then akathisia showed up, so we reduced olanzapine and tried to regulate it with diazepam and biperidene. The reduction of the olanzapine dose provoked relaps of psychotic symptoms. As new adjustment of olanzapine dose resulted with worsening of dyskinesia and akathisia, the patient was admitted to the hospital in January 2008. He was treated with quetiapine and clozapine, supported by biperidene. Psychological examination revealed progressive cognitive decline (attention, intelligence, memory and visuo-motor coordination) due to schizophrenia like psychotic disturbances, with complete social dysfunction. The EEG and CT scan of a brain shown no pathological findings. Neurologic examination was performed and temporary discrete dyskinesia of face and right arm was verified. The neurologist confirmed the existing therapy with recommendation of biperi-

dene augmentation. The patient was released from the hospital with diagnosis of schizophrenia F 20.3. In following months the negative symptoms dominated, with progressive weight loss and worsening of cognitive dysfunction. At the same time, dyskinesia of choreic type with right lateralisation had progressed. The brain MR was done: mild cortical atrophy. Because of unbearable motor dysfunction, the patient showed no more compliance and stopped taking medications. Psychotic symptoms relapsed shortly, but now with bizarre and agitated behavior, hostility, nonsystematic paranoid delusions, suspect hallucinations and completely dezorganised cognitive function. He became chaxectic with further progression of choreo-athetoid involuntary movements, dominantly lateralized in the right with obvious difficulties of movement and gait. The patient was again admitted to the University Department of Psychiatry in October 2008. Further diagnostic exploration was done: CRP, ASL-O, Rheuma factors, Waaler-Rose test, thyroid hormones, complete hematology profile and transaminase were accurate, so EEG as well. The neurologist had considered a possibility of Huntington's disease and suggested genetic typisation. Meanwhile, the patient was released from hospital with clozapine and lamotrigine. Definitive diagnosis of Huntington's disease was confirmed by genetic validation of CAG trinucleotide repeat in size of 16/45. The neurologist recommended haloperidol treatment along with clozapine and lamotrigine as psychiatrist had prescribed. Nowadays, the patient achieved remission of productive psychotic symptoms, with very discrete improvement of cognitive function and slightly reduced generalised choreic hyperkinesia. Athymochormia as a core symptom of schizophrenia still remains.

DISCUSSION

The underlying genetic defect in Huntington's disease is mutation localized on the short end of chromosome 4 and consists of an expansion and instability of polymorphic trinucleotide repeat (CAG repeat) in gene IT15 (Huntington's Disease Collaborative research Group 1993). Penetrance in Huntington's disease is dependent on CAG repeat length (Brinkmann et al. 1997). According to Leavitt et al. 1999, there is a complete penetrance for CAG repeat size of 42, but incomplete of CAG repeat size between 36 and 41. No patient with

clinical diagnosis of HD was found to have a CAG size less than 35. The higher repeat rate correlate with earlier age of onset (Andrew et al. 1993). The genotyping in our patient revealed an expanded allele with 45 CAG repeats (and unaffected allele with 16 repeats), which confirms the diagnosis of Huntington's disease.

Mutation of HD gene results in changes which consist of polyglutamine stretch within the N-terminus of its protein product huntingtin (htt) (Group 1993). This is characterised by two hallmark neuropathological feature: 1.) formation of intraneuronal aggregates containing N-terminal fragments of mutated huntingtin, and 2.) progressive degeneration of striatal neurons (selective atrophy of medium spiny neurons in the caudate and putamen) (Di Figlia et al. 1997). The progression and severity of symptoms was correlated to the rate of striatal neurodegeneration (Aylward et al. 2000). According to Andrews et al. 1999, and Aylward et al. 2004, striatal dysfunctions occur before the clinical symptoms of HD are manifested. There is a loss of large neurons in the deep layers of the frontal and parietal cortex as well (Amann et al. 2000). Neurodegenerative process is probably due to loss of huntingtin's role of up-regulation the transcription of neurotrophic factors which are crucial for neuronal survival (Zuccato et al. 2001). Deficit in memory retrieval in HD is probably due to the decrease in cholinergic activity, while the loss of inhibitory GABAergic function and an increase in dopamine turnover, because of selective survival of type II spiny interneurons, is responsible for the occurrence of psychotic symptoms (Amann et al. 2000).

There are only few cases reported in literature, considering schizophrenia – like psychiatric manifestations in family members affected with Huntington's disease, where these symptoms emerged long before motor or cognitive changes occurred (Lovestone et al. 1996, Tsuang et al. 1998, Tsuang et al. 2000). Correa et al. 2006, described a woman with paranoid schizophrenia-like symptoms and positive genotype for Huntington's disease (43 nucleotide repeats). Authors revealed a three-generation-long family history of chorea and schizophrenia-like psychosis. All subjects had developed psychotic symptoms at least five years before neurological or cognitive manifestations became apparent. Other authors (Schiawach 1994, Zappacosta et al. 1996) consider psychotic symptoms usually rare and non-sistemized and

more connected with the already developed dementia.

Our patient developed psychotic symptoms few years before the neurologic manifestations, while the cognitive decline progressed rapidly. It is hard to say when the side effects of antipsychotic stopped to be side effects and had become the first manifestation of motor disturbances due to Huntington's disease. That could probably be a matter of both conditions. We found no evidence of HD family history. The patient's father died too early and there is still an open question if he would develop HD if he had lived long enough for onset.

So what is the connection between schizophrenia-like psychosis and Huntington's disease? One possibility considers co-occurrence of the HD gene and pro-schizophrenia gene or group of genes, where the HD gene could lower the threshold for onset of schizophrenic phenotype. That is why schizophrenia is more frequent among HD carriers than in the general population (Tsuang et al. 2000). Another option is that in HD families where subjects developed hallucinations and delusions, the HD gene may act as a pro-schizophrenia gene (Correa et al. 2006). Whatever connection there is, there is still the matter of accurate treatment of both entities. The main problem is to choose appropriate medication which would have no negative consequences on the course and the treatment on both disorders. In 2007 Charvin et al, demonstrated that D2 antagonist haloperidol decanoate, which is primarily an antipsychotic, beginning at an early stage can significantly slow down striatal dysfunction in HD (protects striatal neurons from dysfunction induced by mutated huntingtin, and reduces aggregates formation). Our patient, now in treatment with haloperidol, shows so far discrete, but evident therapeutic effect regarding both psychiatric and neurologic symptoms.

CONCLUSION

There is some uncertainty whether schizophrenia - like psychosis in our patient is a genuine entity or just a part of primary Huntington's disease. The role of motor side effects of antipsychotics as attenuating factor for development of neurologic symptoms is dubious as well. Yet those questions made us become aware of high prevalence of overlapping symptoms of both psychiatric and neurologic disorders. Meaning,

therapist has to be very careful regarding therapy management in order to avoid possible complications.

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