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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 atipycal antiypsychotics. Consequently patient developed orofacial diskyinesias which progrediated in unilateral choreo-atetoid 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 resistence on pharmacologic threapy 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

Antypsichotics generally have propensity for numerous side effects. Movement disturbances present most common side effects of typical antipsyhotics 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 blocade of dopaminergic transmission in basal ganglia with consequent hyperactivity of postsynaptic cholinergic neurons (Folnegović-Šmalc et al. 2003, Uzun et al. 2005). Such side effects may cause diffulties in recognizeing 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 & Seller 1993, MacMillian et al. 1993, Quinn & Schrag 1998) Besides abnormal involuntary movement such as chorea, there are abnormalities of volontary 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 concetration (Hayden 1981). The personality changes are the most common behavioural changes, with possible depression, apathy, irritability and agressive manifestation. Schizophrenia-like psychosis occurs with frequency of 6 to 25%, with predominantly paranoid form (Schiawch 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 forthies 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 desease underlying the psychosis.

CASE REPORT

Forty years old male, forestry engineer, divorced, from family not burdened by herritage 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 unsucessfull. He had started drinking and suddenly lost his job. Shortly after he was divorced and separeted 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 seeked. The treatment had begun with first generation antipsychotic flufenazine. Extrapyramidal symptoms (parkinsonisms and temporary distonia) occured in a very short time. No therapeutic answer was accomplished, therefore olanzapine was recommended. In upcoming months cognitive desorganisation and athymochormia persisted and very gradualy 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 monthes 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 wih quetiapine and clozapine, supported by biperidene. Psychological examination revealed progressive cognitive decline (attention, inteligence, 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 preformed and temporary discrete dyskinesia of face and right arm was verifyed. The neurologist confirmed the existing therapy with recommendation of biperidene 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. Becauese of unbearable motor dysfunction, the patient showed no more compliance and stopped taking medications. Psychotic symptoms relapsed shortly, but now with bizzare and agitated behavior, hostility, nonsystematic paranoid delusions, suspect hallucinations and completely dezorganised cognitive function. He became chaxectic with further progression of choreo-athetoid involutory movements, dominantly lateralized in the right with obvious difficultes 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 schiziphrenia 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 expended 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 strech 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 Ayward et al. 2004, strial dysfunctions occure 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 responsibile for the occurence 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 occured (Lovestone et al. 1996, Tsuang et al. 1998, Tsuang et al. 2000). Correa et al. 2006, described a woman with paranoid schizophrenia-like symtoms and positive genotype for Huntington's disease (43 nucleotide repeats). Authors revealed a three-generation-long family history of chorea anf schizophrenia-like psychosis. All sybjects 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 symtoms usually rare and non-sistematized 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 became 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 patients's father died too early and there is still an open question if he would develope 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-occurence 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 signifficantly slow down striatal dysfuntion in HD (protects striatal neurons from dysfuntion 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 shizophrenia - 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 atennuing factor for development of neurologic symptoms is dubios as well. Yet those questions made us become aware of high prevalence of overlaping symptoms of both psychiatric and neurologic disorders. Meaning,

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

REFERENCES

1. *Amann B, Sterr A, Thoma H, Messer T, Kapfhammer HP, Grunze H: Psychopathological changes preceding motor symptoms in Huntington's disease: A report on four cases. World J Biol Psychiatry 2000; 1:55-58.*
2. *Andrew SE, Goldberg YP, Kremer B et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington disease. Nat Genet 1993;4:398-403.*
3. *Andrews TC et al. Huntington's disease progression. PET and clinical observations. Brain 1999;122:2353-2363.*
4. *Aylward EH et al. Onset and rate of striatal atrophy in presymptomatic and symptomatic stages of Huntington's disease. Mov Disord 2000;15:552-560.*
5. *Aylward EH et al. Onset and rate of striatal atrophy in preclinical Huntington's disease. Neurology 2004;63:66-72.*
6. *Brinkman RR, Mezei MM, Thielmann J, Almquist E, Hayden MR. The likelihood of being affected with Huntington disease by aparticular age, for a specific CAG size. Am J Hum Genet 1997;60:1202-1210.*
7. *Charvin D, Roze E, Perrin V, Deyts C, Betuing S, Pages C, Regulier E, Luthi-Carter R, Brouillet E, Deglon N, Caboche J. Haloperidol protects striatal neurons from dysfunction induced by mutated huntingtin in vivo. Neurobiology of Disease 2008;29:22-29.*
8. *Correa BB, Xavier M, Guimaraes J. Association of Huntington's disease and schizophrenia-like psychosis in a Huntington's disease pedigree. Clin Pract Epidemol Ment Health 2006;2:1(ISSN:1745-0179).*
9. *Cummings JL. Behavioural and psychiatric symptoms associated with Huntington's disease. Advances in Neurology 1995;65:179-186.*
10. *DiFiglia M et al. Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science1997;277:1990-1993.*
11. *Folnegović-Šmalc V, Jukić V, Kozumplik O, Uzun S, Mimica N. Side effect profile of atypical antipsychotic agents and comparation to conventional antipsychotics. Soc Psihijat 2003;31:19-24.*
12. *Hayden MR. Huntington's chorea. London: Springer-Verlag, 1981.*
13. *Huntington's Disease Collaborative Research Group: A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 1993;72:971-983.*
14. *Leavitt BR, Wellington CL, Hayden MR. Recent insights into the molecular pathogenesis of Huntington disease. Semin Neurol 1999;19:385-395.*
15. *Lovestone S, Hodgson S, Sham P, Differ A-M, Levy R. Familial presentation of Huntington's disease.J Med Genet 1996;33:128-131.*
16. *MacMillan J, Snell R, Tyler A, Houlihan G, Fenton I, Cheadle J, Lazarou L, Shaw D, Harper P. Molecular analysis and clinical correlations of the Huntington's disease mutation. Lancet 1993;342:954-958.*
17. *Quinn N, Schrag A. Huntington's disease and other choreas. J Neurol 1998;245:709-716.*
18. *Rosenblatt A, Leroi I. Neuropsychiatry of Huntington's disease and other basal ganglia disorders. Psychosomatics 2000;41:24-30.*
19. *Schiwach R. Psychopatology in Huntington's disease patients. Acta Psychiatr Scand 1994;90:241-246.*
20. *Tsuang D, Almqvist EW, Lipe H, Strgar F, DiGiacomo L, Hoff D, Eugenio C, Hayden MR, Bird TD. Familial aggregation on psychotic symptoms in Huntington's disease. Am J Psychiatry 2000;157:1955-1959.*
21. *Tsuang D, DiGiacomo L, Lipe H, Bird TD. Familial aggregation of schizophrenia-like symptoms in Huntington's disease. Am J Med Genet 1998;81:323-327.*
22. *Uzun S, Kozumplik O, Mimica N, Folnegović-Šmalc V. Nuspojave psihofarmaka, Zagreb: Medicinska naklada i Psihijatrijska bolnica Vrapče; 2005.*
23. *Watt DC, Seller A. A clinico-genetic study of psychiatric disorder in Huntington's chorea. Psychol Med Suppl 1993;23:1-46.*
24. *Zappacosta B, Monza D, Meoni C et al. Psychiatric symptoms do not correlate with cognitive decline, motor symptoms or CAG repeat length in Huntington's disease. Arch Neurol 1996;53:493-497.*
25. *Zuccato C, Ciammola A, Rigamonti D, Leavitt B, Goffredo D, Conti L, MacDonald M, Friedlander R, Silani V, Hayden M, Timmusk T, Sipione S, Cattaneo E. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science 2001;293:493-498.*

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