

Patients Review: Drug-Induced Movement Disorders

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ABSTRACT

Objective of this paper is to review drug-induced movement disorders (D-IMD) treated patients on Department of Neurology in University Hospital Osijek. We reviewed patients treated during 10 years period (from 1992 to 2002). Analysed group consisted of 14 patients. Reasons for hospitalisation were swallowing problems in 6 patients, neuroleptic malignant syndrome (NMS) in 3 patients, stroke in 2 patients, bolus choking in 2 patients, and speech disturbance in 1 patient. Working diagnosis for most of our patients was neurological disease, yet only later D-IMD diagnosis was established excluding primary neurological disease, or as associated disease to basic neurological disorder. Nine patients have diagnosed as Parkinson syndrome, 3 patients as NMS, and 4 as orolingual dyskinesia, either autonomously, or in combination with Parkinson syndrome. D-IMD was most frequently caused by neuroleptics. Thus the small number of patients hospitalised regarding this syndrome on Department of Neurology.

Key words: drug-induced movement disorders, Parkinson syndrome, orolingual dyskinesia, neuroleptic malignant syndrome, neurology

Introduction

The objective of the paper is to study drug-induced movement disorders (D-IMD) treated patients on Department of Neurology in University Hospital Osijek during a ten-year period in order to show possible clinical manifestations of the syndrome and to investigate the reasons for D-IMD patients' hospitalization on Department of Neurology, since most frequent D-IMD cause is neuroleptic therapy, and therefore this disorder is in the domain of Department of Psychiatry.

Drug-induced movement disorder is neurologic motoric disturbance caused by drugs. Its features are: abnormally increased motor activity, impaired back posture, abnormally decreased motoric function, mobility and posture. It may be persistent or reversible¹. The most common form is Parkinson syndrome, characterized by bradykinesia, rigidity and tremor². Tardive dyskinesia, akathisia, ticks and dystonia may also be found as part of the syndrome^{3,4,5}. The most severe manifestation is neuroleptic malignant syndrome (NMS) – characterized by severe rigidity, akinesia, hyperthermia, autonomous disturbances, and changes in serum: leukocytosis, ele-

vated sedimentation rate, increase of creatinin-phosphokinase and liver enzymes levels)^{3,4}.

Simultaneous use of different neuroleptics, depot drugs, concurrent lithium therapy, organic brain damage, dehydration and excessive heat exposure and male sex are higher risk factors for NMS³. In general, older, as well as female patients, have more chances to develop D-IMD. It is suspected that there is a hereditary predisposition for D-IMD too⁶.

It is well known that many drugs may cause D-IMD, but some of them are more often charged as guilty for this syndrome. The most common cause of D-IMD is neuroleptic therapy, more often typical neuroleptics in comparison to atypical ones. However, levodopa products, drugs that empty dopamin pools, sedatives, calcium channel blockers, MAO inhibitors, natrium channel blockers, cytostatics, antimycotics, selective serotonin reuptake inhibitors, cholinesterase inhibitors, lithium carbonate and antiepileptics may cause this syndrome as well^{7–11}.

Division to typical and atypical neuroleptics is founded on several factors, among which the most important is affinity toward dopamine D2 system. The affinity toward dopamine D2 system is less prominent in atypical neuroleptics, causing smaller frequency of extrapyramidal side effects.

Duration of D-IMD causing therapy, as well as daily neuroleptic doses aren't correlated with appearance of D-IMD⁶. It is considered that real cause of extrapyramidal symptoms is not only block of dopaminergic receptors, but possible toxic basal ganglia effect is suspected¹². Some of these patients, especially those with NMS are life endangered due to possible myocardial infarction, aspiration pneumonia or rhabdomyolysis with acute renal insufficiency³. Therefore it is very important to suspect and establish correct diagnosis in order to start proper therapy on time and prevent lethal outcome.

Therapeutic approach consists of terminating drugs that are suspected to cause the syndrome, bearing in mind higher risk of worsening symptoms of basic psychiatric disease, use of anticholinergic drugs, and sometimes small doses of dopaminomimetic agents⁷.

Parkinson syndrome usually diminish after the therapy, although, symptoms may persist in some patients in spite of treatment. It is supposed that they had latent or subclinical form of Parkinson disease which manifested after the neuroleptics therapy^{13,14} due to additional effect on basal ganglia.

Materials and Methods

Patients treated on Department of Neurology in University Hospital Osijek which had diagnosis of drug-induced movement disorders were analyzed during 10 years period (from year 1992 to 2002). University hospital Osijek is regional hospital for the East Slavonia and Baranja district. Our hospital covers population of 300,000 people, while the rest of East Slavonian population is covered by general hospitals in Vukovar and Vinkovci. All of our patients come from district of City of Osijek and surroundings.

Disease data were retrieved from patients' records on basis of hospital treated patients index on Department of Neurology. Patients were found in our index regarding discharge letter diagnosis of D-IMD. All the in-hospital patients met the criteria we'd set, and therefore none of them were excluded from the study. Only discharge letter from the Department of Neurology was reviewed per patient during the study period in order to assess the necessary data. Follow-up timeframe was up to patients discharge from the Department of Neurology. Not a single of these patients had more than one hospitalisation on the Department of neurology regarding these disorders. Ambulatory checked and treated patients weren't included in the examination.

Diagnoses of drug-induced movement disorders were made on basis of anamnestic data, neurologic and physical examination and laboratory findings.

Among anamnestic data we searched for suspected drug-induced movement disorders therapy use and duration of that kind of a treatment. Neurological examination revealed extrapyramidal symptoms and signs such as rigidity, bradykinesia, tremor and orolingual dyskinesia. Hyperpyrexia and autonomous disorders (blood pressure and heart rate disorder) were found during the physical examination. Laboratory findings revealed elevated sedimentation rate, increase in leukocytes number, creatinin-phosphokinase and liver enzymes levels.

Reasons for D-IMS patients' hospitalisation and clinical manifestation of extrapyramidal syndrome were analyzed, as well as medicamentous therapy that patients used and which could have caused this syndrome, and time duration from beginning of therapy to extrapyramidal symptoms onset. We studied length of hospitalisation, disease therapy during hospitalisation, course of disease and its final outcome.

Results

Examined group consisted of 14 patients; 8 of them female, 6 male. Average age was 70, 74 in female group, and 69.7 in male, in the range of 55 to 80 (female 55 to 80, male 64 to 75).

Reasons for hospitalisation were swallowing problems (6 patients), malignant neuroleptic syndrome (3 patients), cerebrovascular infarction (2 patients), bolus choking (2 patients), and speech disturbance (1 patient).

In discharge letter 9 patients had diagnosed as Parkinson syndrome, 3 patients as NMS, and 4 as orolingual dyskinesia, either autonomously, or in combination with Parkinson syndrome.

Used drugs analysis showed that D-IMD was most frequently caused by neuroleptics; typical ones: flufenazin and haloperidol used 7 patients, promazine 5 patients, and sulpirid used 1 patient; and atypical ones: clozapin used 2 patients, and 1 patient used olanzapin. Most patients, 5 of them, had monotherapy treatment, 4 patients used two neuroleptics simultaneously, and 4 patients used three kinds of neuroleptics at the same time. Considering other groups of drugs, DIMD was also caused by levodopa in 1 patient, and metoclopramid in 1 patient.

D-IMD presented with different symptoms: 9 patients had Parkinson syndrome, 3 patients had NMS, and 4 patients had orolingual dyskinesia either autonomously, or in combination with Parkinson syndrome.

Time of duration of therapy until symptom onset ranged from 10 days to 22 years. 3 patients developed symptoms in period from 0 to 1 year of drug usage, 5 patients in period of 2 to 10 years, and 3 patients in period 11 to 20 years, and 1 patient in period longer than 20 years. Data of duration of therapy usage before onset of symptoms remained unknown for 2 patients.

During the hospitalisation patients were treated by terminating incriminated drugs therapy, infusion, biperiden, levodopa products and sedatives.

Basic psychiatric disease had worsened in 4 patients, 5 patients presented no changes in extrapyramidal (EP) symptomatology, and decrease of EP symptoms was noticed in 2 patients, while 3 patients fully recovered. Average hospitalisation duration was 14.9 days, in the range of 3 to 24 days. 11 patients were discharged after the end of treatment, 2 patients were transferred to other departments for further treatment, and 1 patient died.

Discussion

Although many drugs may cause extrapyramidal side effects, neuroleptics are the most often cause of D-IMD. Thus the small number of patients hospitalised regarding this syndrome on Department of Neurology. Working diagnosis for most of our patients was neurological disease, yet only later D-IMD diagnosis was established excluding primary neurological disease, or as associated disease to basic neurological disorder. Patients with cerebrovascular infarction had reason for hospitalization on our Department. Later on, during their stay on our department we found out that they also have had the symptoms of drug-induced movement disorders (not related to CVI). Patients with neuroleptic malignant syndrome were hospitalised due to life threatening state and it's emergency on Department of Neurology.

During the almost same time interval (year 1993 to 2002) 45 patients were hospitalised on Department of Psychiatry University Hospital Osijek with D-IMD diagnosis⁵.

D-IMD is more often correlated with typical neuroleptics use during psychiatric disorders treatment^{5,15–18}. Some authors found 30% prevalence of tardive dyskinesia in psychiatric patients using neuroleptics²⁰, while other authors published frequency of 40.6% and 29%^{2,17–19}.

Most of our patients had typical neuroleptics in their therapy protocol. Therapy protocol analysis showed that majority of them had two or three neuroleptics at the same time, while only fewer number of patients were on monotherapy. In case patient had been using just one drug in its therapy, the anamnestic data exposed potential movement disorder causing drug. Otherwise, if more than one neuroleptic was included in patient's treatment, it was impossible to assert the right drug that induced the movement disorder.

It is considered that D-IMD begins as a result of D2 receptor block. However, besides D2 receptors effect, some authors believe that D-IMD develops due to medicamentous toxic effect on basal ganglia^{12,21}. Thus the maintenance of Parkinson syndrome after termination of D-IMD inducing therapy can be explained. Some authors proved correlation between tardive dyskinesia onset and genetic precondition^{7,22,23}.

D-IMD is one of many factors that should influence therapy choice in psychiatric patients. Atypical neu-

roleptics are generally preferred to typical ones due to less extrapyramidal symptoms coincidence, as well as antidyskinetic effects in patients with tardive dyskinesia^{18,24,25}.

Pisa syndrome (rare type of truncal dystonia), sort of D-IMD presentation, develops more often in patients whom had an additional neuroleptic therapy introduced, or patients with increased dosage of neuroleptic⁴. Some authors find correlation between daily neuroleptic dose or depot neuroleptic product use and tardive dyskinesia²⁶, while other authors deny such correlation⁷.

Our data showed that older patients are more prone to development of D-IMD, which is confirmed by other authors^{7,15,17,26}. We haven't been able to analyze neither frequency, nor statistical importance of this disorder considering sex due to small number of patients in our review, although some authors showed not only correlation between DIMD and age and organic injury, but to female sex as well^{4,7}.

Most of our patients developed D-IMD after 2 to 10 years of therapy. The same number of patients used therapy less than one year; and more than 11 years, yet less than 20 years. Hall et al. didn't find correlation between therapy duration and D-IMD⁶.

During hospitalization our patients were treated with anticholinergic agents (biperidine), the ones other authors found successful in D-IMD treatment too^{4,5,18,20}. Drugs caused dystonia diminished after anticholinergic agent therapy only in 40% of cases, while the same therapy showed better results in cases of symptoms of idiopathic dystoniae⁴. We also used infusion, levodopa products and sedatives, while D-IMD inducing drugs therapy was terminated. In some cases clozapin was proved as successful therapy in tardive dyskinesia treatment²⁴. Effect of donezepil, a cholinesterase inhibitor, used in dementia treatment is being studied²⁷.

Current D-IMD therapy model results are still unsatisfactory. It is noticed that there are always differences in therapy response between two different clinical D-IMD manifestations. Reports show that tardive dyskinesia is much less responsive to therapy than dystonia⁴.

Most of our patients showed progression of psychiatric symptoms, or no regression of extrapyramidal symptoms at all, during the treatment. Only less number of patients fully recovered, or showed decrease of D-IMD symptoms. One third of patients had dyskinesiae even one year after ending of neuroleptic therapy²⁸. Tardive dyskinesia treatment discouraging, therefore it emphasizes prevention of this syndrome by carefully choosing atypical neuroleptic²⁹, or, switching from typical to atypical neuroleptics in case of already developed extrapyramidal symptoms³⁰.

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PRIKAZ PACIJENATA: JATROGENI EKSTRAPIRAMIDNI SINDROM

SAŽETAK

Cilj rada bio je prikazati bolesnike liječene od jatrogenog ekstrapiramidnog sindroma (D-IMD) na Klinici za neurologiju Kliničke bolnice Osijek. Prikazali smo bolesnike liječene u periodu od 10 godina (od 1992–2002. god.). U analiziranoj skupini je bilo 14 bolesnika. Razlozi za hospitalizaciju bili su u 6 bolesnika smetnje gutanja, u 3 bolesnika neuroleptički maligni sindrom (NMS), 2 bolesnika su bila hospitalizirana zbog moždanog udara, 2 bolesnika imala su gušenje bolusom hrane i u 1 bolesnika su bile prisutne smetnje govora. Radna dijagnoza za većinu pacijenata bila je neurološka bolest, tek je kasnije postavljena dijagnoza D-IMD, isključenjem primarne neurološke bolesti ili kao pridruženi poremećaj osnovnoj neurološkoj bolesti. Devet pacijenata dijagnosticirano je kao Parkinsonov sindrom, 3 kao NMS, a 4 kao orolingvalne diskinezije samostalno ili u kombinaciji sa Parkinsonovim sindromom. D-IMD je najčešće uzrokovan neurolepticima. Time objašnjavamo mali broj hospitaliziranih bolesnika zbog ovog sindroma na Klinici za neurologiju.