EXTRAPYRAMIDAL SYNDROMES CAUSED BY ANTIPIPSYCHOTICS

EKSTRAPirimidalni sindromi izazvani antipsihoticima

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Summary

Introduction. Extrapyramidal syndromes are significant side effects of antipsychotic therapy due to their severity, frequent occurrence and complications. This paper gives a brief summary of the literature with the emphasis on epidemiology, etiology, diagnosis and differential diagnosis, as well as the treatment of extrapyramidal disorders induced by antipsychotics. Dystonia. Sustained muscle contractions cause twisting and repetitive movements or abnormal postures. It may appear either as an acute or delayed, i.e. tardive sign. The incidence of dystonia is 2-3% among the patients treated with antipsychotics, and 50% among the ones cured with conventional antipsychotics. Akathisia. The main feature of this curious adverse effect is the psychomotor restlessness and the inability to remain motionless. Although akathisia is not very frequent, its incidence and prevalence ranges from 5 to 50% among the treated patients. It is most probably a result of the blockage of dopaminergic receptors. Parkinsonism. The most frequent secondary Parkinsonism is the one caused by drugs. The characteristic parkinsonian signs regress 4 to 16 weeks after the discontinuation of antipsychotic therapy. In the era of atypical antipsychotics this adverse effect appears less frequently. Tardive dyskinesia. Involuntary choreatic movements or abnormal posture may appear days and months after the introduction of continuous use of antipsychotics. The individual susceptibility may play the major role in the development of this side effect. Conclusion. Numerous studies have compared conventional and atypical antipsychotics as well as atypical ones with one another in order to decrease the risk of development of extrapyramidal side effects as well as to prevent their occurrence and improve their treatment. Keywords: Basal Ganglia Diseases; Extrapyramidal Tracts; Antipsychotic Agents + adverse effects; Dyskinesias; Dystonia; Psychomotor Agitation; Parkinsonian Disorders

Introduction

Movement disorders associated with the use of antipsychotic therapy have an important place in clinical practice, and are thus classified as a separate diagnostic category in the classification system of mental disorders (Diagnostic and Statistical Manual of Mental Disorders - DSM IV) (1994) and extrapyramidal syndromes (EPS) are classi-
Abbreviations:

EPS − extrapyramidal syndromes
AP − antipsychotic
CAP − conventional antipsychotics
AAP − atypical antipsychotics
ADR − acute dystonic reaction
TD − tardive dyskinesia

Antipsychotic (AP) therapy-induced EPS include a variety of iatrogenic-induced movement disorders which can be divided into acute and tardive syndromes. Acute EPS are those that develop within hours or weeks after initiating or increasing doses of AP and they include acute dystonia, akathisia and Parkinsonism. Tardive dyskinesia and tardive dystonia are delayed-onset syndromes and usually develop after a prolonged use of AP.

Neuroleptic malignant syndrome is an idiosyncratic, potentially life-threatening and often diagnostically unrecognized condition induced by AP, which manifests with sudden fever, autonomic nervous system instability, EPS and altered state of consciousness. It is often accompanied by elevated serum creatine kinase levels, impaired liver and renal function, leukocytosis, disturbed electrolyte balance and coagulation, as well as ECG changes [1]. Due to its uniqueness in terms of complexity of the clinical picture, diagnosis and therapeutic approach, neuroleptic malignant syndrome will not be covered by this text [2-4].

The term "neuroleptic", meaning "to fix or hold a neuron," was used to describe the neurological adverse effect of conventional antipsychotics (CAP) rather than their therapeutic effects. In earlier clinical practice, the procedure for treating the patients with psychotic disorders was increasing the dose of CAP to the so-called "neuroleptic threshold," i.e. the dose when EPS occurs, and waiting for the therapeutic response. The attitudes have changed due to the appearance of atypical antipsychotics (AAP): clozapine, risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. The main characteristic of AAP is a reduced risk of both acute and tardive EPS [5,6]. It is also one of their main characteristics and advantages associated with better treatment acceptance and compliance. Some of them, such as clozapine, have proved to be effective for the treatment of resistant patients, and less commonly cause increased serum concentrations of prolactin [7].

It is believed that antagonism of dopamine D2 receptors is involved not only in antipsychotic effects, but also in causing EPS. Studies in which positron emission tomography (PET) was used have shown that antagonism of 60-70% of dopamine D2 receptors is required for CAP to be effective, and 75-80% of D2 receptor blockade leads to the occurrence of acute EPS [8,9]. Most authors estimate that EPS appear in about 90% of patients treated with CAP, such as haloperidol, in which the therapeutic range is the narrowest and therapeutic activity and EPS mutually inseparable [6,10]. The use of second generation antipsychotics, in particular clozapine, is associated with a lower risk of movement disorders, compared to the use of CAP [11,12]. Goldstein [13] points out that long-standing use of clozapine was not associated with increased occurrence of tardive dyskinesia, dystonia, akathisia and Parkinsonism.

The mechanism of "atypicality" of new-generation antipsychotics is still being discussed. Some authors believe that this is a consequence of pharmacodynamic characteristics of AAP, such as increased antiserotonergic, anticholinergic activity, along with antidopaminergic one [14]. Others argue that the difference is primarily in the pharmacodynamics, due to not so strong and transient binding to D2 receptors which are atypical when compared to conventional AP [15]. D2 receptors are least occupied dose-independently by clozapine and quetiapine at therapeutic values, which are, therefore, associated with the lowest risk of EPS [9,16,17]. Kane [6] states that quetiapine is a new-generation antipsychotic with the most desirable profile of adverse neurological effects since the incidence of EPS is reduced to the level of placebo, even at high therapeutic doses. Unlike clozapine and quetiapine, risperidone and olanzapine show a greater tendency to striatal D2 receptors, leading to the more frequent occurrence of EPS. Although they have a higher affinity for 5-HT2A receptors, at higher doses they induce the occurrence of EPS more frequently. There are few comparable data available for assessing the risks carried by AAP for the induction of EPS, but, the order is as follows according to Tarsy [14]: clozapine <quetiapine<olanzapine. At doses higher than 8mg/day risperidone carries a greater risk compared to olanzapine. The superiority of AAP comes mainly from the comparisons with inappropriately high doses of CAP; primarily haloperidol. In clinical practice, AAP doses are increasingly elevated, with the exception of risperidone; thus the possibility to balance the risks of EPS in future is greater.

In spite of being significantly reduced, the risk of inducing EPS associated with the use of AAP does exist; hence the need for further research directed towards the treatment of choice has arisen.

Metabolic syndrome, also called "EPS of the new millennium" is an extremely significant side effect of AAP [18]. There is no doubt that the risk of weight gain, impaired glucose tolerance, hyperlipoproteinemia, hypertension, increased risk of diabetes and cardiovascular disorders affects the choice of an antipsychotic drug that is to be introduced into therapy.

Dystonia

Dystonia is a short or prolonged muscle contraction which leads to abnormal movement or posture. Unlike an acute dystonic reaction (ADR), in which a muscle contraction is transient, in tardive dystonia it is persistent and usually occurs after years of use of antipsychotics, but may also occur after a significant-
ly shorter exposure to AP therapy. Antipsychotic-induced dystonia is typically focal, although in rare cases it can affect several muscle groups. It manifests in the cranial, pharyngeal, cervical and axial muscles leading to oculogyric crisis, stiff jaw, tongue protrusion, torticollis, retrocollis, laryngeal, pharyngeal spasm, dysarthria, dysphagia, and sometimes difficulties in breathing, cyanosis, opisthotonus. Limb muscles are less commonly affected; hence tardive dystonia is sub-classified as dyskinesia by some authors [19]. Dystonia is a very unpleasant experience for patients, sometimes even painful.

Of all patients treated with neuroleptics, about 2-3% will develop ADR in the first few days after starting the drug [20]. If a highly potent classical AP is used, that percentage can increase up to 50% [20]. Half of the ADR reported cases is described in the first 2 days of exposure to AP, and 90% in the first 4 days [21]. Daily rhythm with a significantly higher incidence in the second half of the day was also observed [20].

Risk factors include primarily the duration of use and high dose of AP, younger age, male gender, mental retardation, positive family history of dystonia, previous dystonic reaction, a recent cocaine and alcohol abuse [21]. Dystonia can sometimes be caused by antiemetics and some antidepressants. All antipsychotic drugs, including AAP, may lead to dystonia, although it seems that they are less common with the use of antipsychotic drugs having a more pronounced anticholinergic action. The duration of dystonia may be prolonged when depot preparations of antipsychotics are used.

The pathogenesis is still unclear, although it is associated with secondary hypersensitivity of blocked D2 receptors.

When diagnosing neuroleptic therapy-induced dystonia, it is important to exclude neurological disorders that can also be the cause. An inexperienced doctor can often misinterpret this phenomenon as histrionic behavior.

Tardive dystonia varies differentially diagnostically from tardive dyskinesia not only because of its phenomenology, but also because it is more common in younger people in whom it may be alleviated by the use of anticholinergics, unlike tardive dyskinesia which may even be aggravated [22].

Despite the unclear pathophysiology, treatment with ADR is very successful. Intravenous use of anticholinergics is effective and fast acting and the result is sometimes achieved within minutes. The recommended initial dose of biperiden is 2 mg parenterally and 2mg per os, with a dose of 2mg/day per os in the next 1-2 weeks. The preventive use of anticholinergics is justified in patients at higher risk (younger men and those with previous ADR experience) [20]. If ADR is not treated, it can last for hours or days. When antipsychotic therapy is required, atypical group is indicated, such as aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone, which showed a lower risk of inducing EPS, particularly acute dystonia and Parkinsonism. In case of tardive dystonia, a change of antipsychotic is indicated – the introduction of clozapine is recommended, and sometimes the application of high doses of anticholinergics, such as trihexyphenidyl, may be effective [23]. Blockade of motor neurotransmission with Botulinum toxin in the affected muscles is successful in patients, but the improvement is usually only temporary [24]. There is a possibility of spontaneous remission, but in most cases, dystonia persists for years and is extremely debilitating and stigmatizing. Data from the literature point to the effectiveness of other medicament and non-medicament procedures in the treatment of tardive dystonia, such as tetrabenazine, reserpine, procyclidine, benzotropine, baclofen, deep brain stimulation, levodopa and physiotherapy.

**Akathisia**

The term akathisia was first mentioned by Haskovec in 1903 and the question whether it is a movement disorder, mental disorder or both arose at the beginning of the twentieth century [25].

Akathisia is a frequent and serious adverse effect of treatment with antipsychotic drugs. It includes half of EPS [21] and is considered one of the most common movement disorders induced by blocking dopamine receptors with neuroleptics and antiemetics [20]. Akathisia may also be caused by serotoninergic agents, serotonin reuptake inhibitors and cocaine.

This syndrome consists of a subjective and objective component. The patients suffer from the feeling of restlessness and an irresistible urge to move. They describe a very upsetting experience of pressure, nervousness and tension. Objectively, an increased motor activity consisting of complex, often meaningless stereotyped and repetitive movements is recorded. Motor restlessness is typically expressed as full body movements, but sometimes only as "restless legs" in the form of myoclonus of the feet. The patients cross and uncross their legs, fidget in a chair or bed, hop, stand up and soon return to the previous position, walk as if marching on the spot.

According to the time of onset in relation to the initiation or increase of AP therapy and duration of symptoms, akathisia can be divided into acute, tardive, chronic and withdrawal akathisia following the discontinuation of AP. Acute akathisia occurs shortly after the initiation or increased dose of AP within two weeks, and tardive akathisia develops after at least three months of therapy, regardless of the change in an antipsychotic drug or its dose. Acute and tardive akathisia as well as akathisia following the discontinuation of AP can persist for more than 3 months, which leads to chronic akathisia [26]. The aforementioned forms of akathisia do not differ significantly from acute akathisia in objective motor symptoms, whereas the subjective component may be less pronounced over time.

Data on the incidence and prevalence are inconsistent due to different diagnostic approaches [26]. The prevalence of akathisia varies widely from 5 to 36.8%. Acute akathisia occurs in 25% of patients...
treated with an antipsychotic [21]. Data from CATIE show that akathisia occurs in 10 to 20% of patients treated with atypical AP, which is less than 20 to 52% when typical neuroleptics are used [21]. No significant evidence of age and gender such as a predisposition has been found [21,26]. There is a correlation between the neuroleptic potency for D2 receptors and doses in relation to how pronounced symptoms of akathisia are [20].

Pathophysiological mechanism of akathisia is still unclear [26]. Some authors believe that the diagnosis of akathisia can be made solely on the basis of movement disorders, while others point out their existence as a mechanism by means of which the patients struggle and reduce the feeling of restlessness and urge to move. However, the proper diagnosis of this problem according to the current criteria requires both objective and subjective component. In the case of the motor component alone, some authors regard pseudoakathisia as tardive dyskinesia of the lower extremities [26]. Others classify pseudoakathisia into a subcategory of true akathisia with less pronounced symptoms, the objective component being dominant [26]. Doctors sometimes misinterpret this condition as psychotic agitation, and thus promptly introduce an antipsychotic and thereby worsen or prolong this condition. Since the subjective component of akathisia may lead a patient to suicide, this situation must not be ignored or remain unrecognized.

Akathisia may persist for the duration of antipsychotic therapy, and usually ceases after the discontinuation of AP. Therefore, when treating akathisia, the dose of AP should preferably be reduced first or an atypical drug should be chosen. Clozapine and quetiapine proved to carry the lowest risk in causing akathisia [21]. The symptoms of akathisia can also be reduced by nonselective liposoluble β-blockers (propranol initially 30mg/day in three doses, with gradual increase to 120mg/day, if necessary) [26]. Benzodiazepines (lorazepam 1.5-3mg/day and clonazepam 0.5mg/day) are also indicated, especially in the case of persistent subjective symptoms [26]. Clonazepam may be preferable to diazepam due to its long half-life. Effectiveness of anticholinergics has not been confirmed [26]. Clonidine has shown a positive effect, but its use is associated with serious side effects such as sedation and orthostatic hypotension [26].

Research on the effectiveness of amantadine, ritalinserin and piracetam is currently underway.

**Antipsychotic-induced Parkinsonism**

Drug-induced Parkinsonism is the second most common form of Parkinsonism in elderly people after idiopathic Parkinson's disease. The interval between the application of the drug and the onset of Parkinsonism is variable and ranges from a few days to several months.

Unlike Parkinson's disease, the symptoms are often bilateral and symmetrical. There is a triad of bradykinesia, muscle rigidity and tremor, although it is usually less pronounced. Other symptoms and signs include unsteady gait, festination, reduced synergia, anteropulsion, hypomimia, sialorrhea and seborrhea. Postural tremor is more common than resting tremor. Tremor of the lips and perioral muscles can be observed as well, which is also called ‘rabbit syndrome’.

In patients who have used AP, the prevalence is about 15%, although it is difficult to determine with precision due to the fact that epidemiological studies usually classify it as a form of Parkinsonism or generally drug-induced movement disorder [27].

Risk factors include: age, female gender, type of drug used, dose and duration of therapy, cognitive deficit, acquired immunodeficiency syndrome, tardive dyskinesia and early-onset extrapyramidal disorder [27].

Pathophysiological mechanism is associated with dopaminergic D2 and serotonergic 5-HT2A receptors blockade and low affinity of particular AP to acetylcholine receptors.

Although drug-induced Parkinsonism is considered a reversible condition, in most cases it usually lasts up to 4 months, it can last 6-18 months, and in 15% of cases it has been even described as persistent [27]. In case of persistent symptoms, antipsychotic-induced Parkinson's disease should be taken into consideration, and it should be treated with dopaminergics. Symmetrical postural tremor associated with drug-induced Parkinson's disease can be mistaken for essential tremor in the elderly which is mono-symptomatic. Information on taking AP, coexistence of orofacial dyskinesia, limb muscles dyskinesia and akathisia may be helpful for the proper diagnosis. Since there is no nigrostriatal degeneration as with Parkinson's disease, Dopamine Transport SPECT Imaging (DaTscan) does not record a reduced dopamine reuptake in case of drug induced-Parkinsonism. When the differential diagnosis is being made in relation to vascular Parkinsonism, which is usually also symmetrical, the history of previous vascular incident, as well as risk factors for cerebrovascular diseases should be taken into consideration.

Bearing in mind that the quality of life of patients with symptoms of drug induced-Parkinsonism declines drastically, and that its course is usually reversible, it is of high importance to recognize this condition early and employ appropriate therapeutic measures. The first step in treating patients is to reduce the dose of antipsychotic drugs (if possible) or substitute the applied AP with another, usually atypical one. The treatment of choice does not really exist, although the use of anticholinergics is a part of everyday practice often with favorable results [27]. They should be avoided in the elderly because of adverse effects such as deterioration in cognitive function, urinary infection, closed-angle glaucoma precipitation. Acetylcholinesterase inhibitors may serve as an alternative. Amantadine has proved successful so far only in small studies, although it is not well-tolerated by elderly patients [27]. The use of dopaminergic drugs is
not justified in this type of Parkinsonism. Clozapine and quetiapine have a significant advantage in the treatment of psychotic symptoms in Parkinson’s disease compared to other atypical and typical antipsychotics [27]. In case of the discontinuation of AP, the symptoms may last from 2 weeks up to 3 months in elderly patients. In them anticholinergic therapy can be continued until these symptoms have completely disappeared [28].

**Tardive dyskinesia**

It is manifested by involuntary choreoathetoid movements of the orofacial region, extremities, trunk and respiratory muscles. The movements are more pronounced with excitement, and disappear during sleep. Sometimes the patients set up their mind to decrease the intensity of the involuntary movements and succeed in doing so, but for a short time. It should be noted that a significant number of patients do not notice these involuntary movements or are not bothered by them [29]. It is family who is usually upset more than the patients themselves.

Tardive dyskinesia (TD) can occur in all patients treated with AP [12]. It develops after months or years of continuous use of antipsychotics. The condition can also persist after the discontinuation of AP or may even be irreversible.

The incidence of TD associated with CAP therapy in long-term studies is 5% per year in adults [14] and cumulative annually 25-30% in the elderly [17]. With atypical AP treatment, the incidence is significantly lower [12]. When risperidone and olanzapine are used [21], the incidence becomes the same as the incidence of spontaneous TD in patients with schizophrenia. Some extremely rare cases were described resulting from the use of clozapine [30].

The incidence of TD varies depending on the type and dose of AP, duration of use, gender, patient’s age, although there is a belief that most patients will develop TD if treated long enough. Elderly patients as well as female patients are at a greater risk [29]. Risk factors also include brain damage, dementia, mood disorders, duration of AP therapy, use of anticholinergic antiparkinsonian therapy, previous occurrence of EPS.

The early occurrence of EPS, being non-Caucasian in race, older age, genetic predisposition to develop schizophrenia and the occurrence of TD as a side effect of AP are mentioned as the leading risk factors for the occurrence of TD in schizophrenic patients [31]. The correlation between early EPS and TD may be an indicator of individual variations in susceptibility of dopamine system, and therefore a possible early form of prevention of TD by the right choice of AP.

Kane [6] found the greater tendency of patients suffering from mood disorders to develop tardive dyskinesias than those with schizophrenia. Bleuler [32] and Kraepelin [33] noted as early as the pre-antipsychotic era that tardive dyskinesia could occur spontaneously in patients with psychosis. These observations have been confirmed by modern research [14]. Tenback [31] mentions the occurrence of spontaneous TD more commonly in schizophrenic patients not treated with AP as well as in their first degree relatives, and states that TD may be associated with genetic vulnerability for the occurrence of schizophrenia.

Spontaneous TD occurs in about 0.5% per year of age in the general "non-psychiatric" population after the age of 60 [21]. There is also higher, but very variable prevalence of orofacial dyskinesias in the elderly demented people, with or without psychotic disorders or mood disorders.

There are data from small studies on genetic vulnerability as a risk factor and the dopamine D2 receptor gene DRD2 as a predisposition for the development of TD in patients with schizophrenia [34].

TD is associated with increased mortality and higher incidence of respiratory infections.

Pathophysiologically most convincing evidence suggests that TD is a result of primarily neuroleptics-induced dose-dependent super-sensitivity of D2 receptors in the nigrostriatal pathway.

Should TD occur, it would be indicated to discontinue AP. However, many patients require the continuation of this therapy. In that case the dose of CAP should be reduced to the minimum effective dose and/or replaced with an antipsychotic whose administration carries the lowest risk of TD, such as clozapine [23] or quetiapine [6]. The use of vitamin E, valproates, essential fatty acids and benzodiazepines has also been considered, but the evidence is inconclusive for any of the above options [29].

**Conclusion**

Extrapyramidal syndromes are frequent, severe, debilitating and stigmatizing consequences of neuroleptic therapy. In recent years conventional antipsychotics have been replaced by the atypical ones in the therapeutic approach primarily due to reduced risk of causing both acute and tardive extrapyramidal syndrome. Since atypical antipsychotics represent a new generation, longer studies regarding the mentioned risks are necessary, especially when it comes to tardive movement disorders. In spite of having many benefits, the adverse effects of atypical antipsychotic drugs are far from negligible. Metabolic syndrome, also known as “extrapyramidal syndrome of the new millennium”, can be more important compared to the involuntary movement disorders in terms of morbidity, disability and mortality. Treatment of certain iatrogenically induced extrapyramidal syndrome with anticholinergics, beta blockers, anxiolytics and other aforementioned drugs and methods has shown good, but not always completely successful results. Therefore, further research is required with the hope to improve prevention and diagnosis, reduce or eliminate unwanted symptoms already manifested and the recurrence of extrapyramidal syndrome in the patients with previous experience of this stigmatizing and very important side effect in the treatment of primary disorder.
References


Recenziran 11. XII 2011.
Prihvaćen za štampu 7. IV 2012.

Poznić Ješić M, et al. Extrapyramidal syndromes caused by antipsychotics