Drug-induced dystonia

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Drug-induced dystonia (DID) is a rarely diagnosed adverse reaction to a sufficiently large number of drugs. Acute DID (ADID) occurs soon after starting to take a drug or raising its dose, and switching from one antipsychotic medication to another, especially to its injectable dosage form. Tardive DID (TDID) develops a few months or years after starting drug intake or 3 months after stopping therapy. The diagnosis of TDID is based on the persistence of dystonic hyperkinesis for more than 1 month, the use of a dopamine receptor blocking agent, and the absence of other causes of its development. The risk factors for DID are male sex; young age (less than 30 years of age); a history of dystonic reactions; hypocalcemia, alcohol use while taking the drug. DID is most commonly related to therapy with antipsychotics, metoclopramide, antidepressants, and antiepileptic drugs. The short-term use of anticholinergic drugs (benzotropin, diphenhydramine) is effective in treating ADID. Anticholinergic drugs and atypical antipsychotics (clozapine, quetiapine), benzodiazepines, muscle relaxants (baclofen), and dopamine reuptake inhibitors (tetrabenazine) are used to treat TDID. To prevent DID, it is very important that a physician should be aware of that this unwanted adverse reaction may occur and that a drug with the lowest risk for DID should be chosen.

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Drug-induced dystonia (DID) is a rarely diagnosed adverse drug reaction (ADR) of a fairly large number of drugs [1].

Clinical features

Acute DID (ADID) occurs shortly after a drug administration or an increase in its dose, as well as after switching from one antipsychotic drug to another, especially to the injectable form [1]. In a half of the patients the first symptoms of ADID can develop 2–5 days after the drug administration [1, 2]. Dystonia may vary in severity, involve different body regions, and is usually painful [1]. The most common forms are orofacial, truncal and cervical dystonias; however, the classic manifestations of ADID usually include oculogyric crises (conjugate involuntary deviation of the eyes upward or laterally) lasting from several minutes to several hours, opisthotonus or extensor axial dystonia (involuntary backward deviation of the head, neck and back), and oromandibular dystonia (involuntary muscle contractions of the lower jaw, making it difficult to open or close the mouth) [1, 2]. Blepharospasm, trismus, laryngeal dystonia, tongue protrusion and respiratory dystonia may also occur. Symptoms are usually painful and worsen when walking, forced breathing, talking, and swallowing. In severe cases, such as laryngospasm, ADID can be a life – threatening condition. Sustained muscle contraction can also lead to rhabdomyolysis. Bizarre postures in patients with dystonia may be misdiagnosed as hysterical; since dystonia often occurs in patients with mental diseases, it can be mistakenly identified as catatonia. Unlike patients with catatonia, patients with ADID are actively complaining and seek for help. Unfortunately, after an attack of acute dystonia, such patients often refuse treatment for the underlying mental disease. Neuroleptic malignant syndrome may be diagnosed in the case of an increase in body temperature, development of generalized muscle rigidity, impaired consciousness, instability of the cardiovascular and respiratory systems. [1].

Tardive DID (TDID) became distinguished as an independent nosological unit in 1982, after R.E. Burke et al. [3] had described 42 patients with this disorder.

TDID occurs several months or years after the drug administration or 3 months after the drug discontinuation [1, 2]. TDID is diagnosed based on the persistence of dystonic hyperkinesis for more than 1 month, history of dopamine receptor-blocking drug intake, and lack of other causes of dystonia (e.g. hereditary dystonias, lesions in basal ganglia, etc.) [1]. Unlike ADID, symptoms of TDID develop gradually over weeks or months. Remission periods are uncommon. The symptoms may not be painful and may be present in one part of the body or progress to other body parts and even become generalized (which is more typical of younger patients). Patients often notice an increase in the severity of symptoms depending on the emotional state, which leads to variability in the manifestations of hyperkinesis during the day.

Cervical TDID is extremely similar to idiopathic cervical dystonia – involuntary muscle contractions lead to pathological postures of the head and the neck, that can be accompanied by tremor. While the most common form of idiopathic cervical dystonia is torticollis, patients with TDID present with retrocollis. The clinical severity varies from minimal to severe deviation and may be accompanied by pain and dystonic tremor.

The combination of oromandibular dystonia and blepharospasm is called Meige syndrome. Tardive oromandibular dystonia (TOD) is characterized by difficulties in opening and closing the mouth and impairs chewing, speech and swallowing. Bruxism is frequently seen in patients with jaw-closing oromandibular dystonia. Pisa syndrome is one of the forms of axial dystonia associated with antipsychotics and is defined as involuntary lateral bending of the trunk (lateroflexion) [4]. This syn-

drome is more common in older patients, especially in women receiving a combination of antipsychotics, and patients with organic brain disorders such as dementia. [5]. Pisa syndrome can present either as an acute emergency or develop gradually over time. Unlike tardive dystonia, the Pisa syndrome severity decreases or may even resolve after the discontinuation of the drug. Consequently, Pisa syndrome can be considered as an atypical form of tardive dystonia. Rarely, patients with tardive dystonia may have a life-threatening condition with severe dystonic spasms that lead to rhabdomyolysis, myoglobinuria, and acute renal failure.

Prevalence and risk factors

Assessment of the prevalence of DID is difficult due to high heterogeneity of associated risk factors, drug classes and dosages. Thus, in patients treated with antipsychotics it can reach 5% [6]. Among patients who are prescribed an antipsychotic for the first time, ADID prevalence varies from 34% to 60% [7]. DID risk factors include male sex, younger age (<30 years), history of dystonic reactions, hypocalcemia, simultaneous use of alcohol and prescription drugs [6, 8].

Medications, associated with the development of DID and the underlying mechanisms

Different drugs associated with the development of DID and their underlying mechanisms are presented in the Table.

Antipsychotics

Antipsychotics are among the most commonly reported causes of DID due to their ability to bind to dopamine D2 receptors of the corpus striatum. Antipsychotics are associated with both ADID and TDID. DID may also occur after antipsychotics discontinuation [1, 9]. In a prospective study [10] (246 neuroleptic-naive patients with acute psychosis) ADID in patients treated with risperidone (median dose 3.2 mg) occurred in 26.4% of cases, which did not significantly differ from its incidence in the haloperidol group (34.5%). In the meta-analysis of randomized controlled trials, ADID incidence in patients aged <18 years treated with aripiprazole did not significantly differ from placebo [11]. In the meta-analysis of Cochrane systematic

Table. Drugs associated with DID [1, 6–32]

Drug class / drug	Prevalence (incidence), %	Pathophysiological mechanisms	Level of evidence
Antipsychotics:			
amisulpride	6.4	Dopamine receptor blockade	B
aripiprazole	5.5		B
asenapine	2.8		B
chlorpromazine	10.9		B
haloperidol	16.5		B
olanzapine	1.6		A
paliperidone	2.4		B
quetiapine	1.4		B
risperidone	5		B
sulpiride	15.3		B
ziprasidone	2.2		B
droperidol	3.8		A
Metoclopramide	0.2	As above	A
Antidepressants			
Selective serotonin reuptake inhibitors:			
fluoxetine	Unknown	5-HT2 receptors hyperstimulation, inhibition of dopaminergic activity	C
citalopram	« «		C
fluvoxamine	« «		C
escitalopram	« «		C
paroxetine	« «		C
sertraline	« «		C
Tricyclic antidepressants:			
imipramine	Unknown	Unknown	C
amitriptyline	« «	« «	C
Selective serotonin-norepinephrine reuptake Inhibitors:			
venlafaxine	Unknown	Slow metabolism in patients with CYP2D6 gene polymorphism	C
Anticonvulsants			
carbamazepine	Unknown	Desensitization of presynaptic dopamine receptors	C
gabapentin	« «	Unknown	C
lamotrigine	« «	« «	C

Other drugs			
metformin	Unknown	Unknown	C
lamivudine	« «	« «	C
rivastigmine	« «	« «	C
albendazole	« «	« «	C

Note. 5-HT2 –a subfamily of serotonin receptors, i.e., receptors that bind to the endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT); CYP2D6 – cytochrome P450 2D6. Level of evidence [1]: A – one or more randomized controlled trials; B – non-randomized controlled studies, prospective observational studies, cohort studies, retrospective studies, case-control studies, meta-analysis and/or postmarketing studies; C – presence of at least one case report or case series.

reviews [12] ADID was less frequent in patients treated with olanzapine, quetiapine and ziprasidone, compared with haloperidol and chlorpromazine treatment.

Metoclopramide

Metoclopramide is associated with a variety of movement disorders, including DID, though they are not frequent. DID prevalence is higher in children and older patients and can reach 25% [13]. Children have a 6-fold increased risk of ADID compared with adult patients [14].

Antidepressants

DID is a relatively rare ADR in patients treated with antidepressants. According to an Austrian study, which analyzed movement disorders occurrence in patients with mental diseases treated with antidepressants, only 3 out of 243 588 patients developed DID from 1993 to 2015 [15].

DID is associated with a considerable number of drugs (see the Table). This ADR is mainly described in patients with mental disorders as case reports [7]. Frequently ADID is associated with different selective serotonin reuptake inhibitors [15]. ADID associated with fluoxetine is primary reported in patients receiving combination treatment with antipsychotics [16]. ADID associated with tricyclic antidepressants is reported in children treated with imipramine for nocturnal enuresis [17], and TDID in young men treated with 50 mg of amitriptyline for depression [18, 19]. Several authors also reported ADID after the administration of selective serotonin-norepinephrine reuptake inhibitor – venlafaxine [20, 21].

Anticonvulsants

In a prospective study DID was present in 4 out of 201 patients with epilepsy treated with anticonvulsants [22]. DID potentially may be associated with gabapentin [23] and carbamazepine [24]. Several authors reported both ADID [24] and TDID [25] in children and adolescents treated with carbamazepine. Several case reports described ADID in older patients treated for essential tremor with a combination of gabapentin and propranolol [23, 26]. TDID may also occur in patients treated with lamotrigine [27]. Underlying mechanism of DID associated with anticonvulsants is not clear. For instance, DID in patients treated with carbamazepine can occur in both normal and toxic serum drug levels [28].

Other drugs

One case report described ADID in a female patient with schizophrenia after she was prescribed 500 mg of metformin in addition to her routine therapy (sulpiride 800 mg/day, clozapine 300 mg/day) [29]. The authors concluded that DID was a result of the drug interaction between metformin and sulpiride. There are also several case reports of ADID and TDID in young men treated for hepatitis B with lamivudine [30]. A single case report described ADID in an older female patient with Alzheimer's disease associated with transdermal rivastigmine patch (10 mg/cm2) [31]. ADID was also reported in a child treated with a combination of albendazole and cetirizine [32].

Treatment

A short-course treatment with anticholinergic drugs (benztropine, diphenhydramine) is effective in patients with ADID [1, 33]. In case a patient develops a life-threatening condition (e.g. laryngospasm), parenteral anticholinergic drug administration is required, tracheostomy may be performed, if necessary [1, 33]. Benzodiazepines can be used to reduce the severity of anxiety disorders [1, 33].

Treatment of TDID also includes anticholinergic drugs, atypical antipsychotics (clozapine, quetiapine), benzodiazepines, muscle relaxant agents (baclofen), drugs that inhibit dopamine reuptake (tetrabenazine). Amantadine, beta-blockers, clonidine, dantrolene, levodopa and anticonvulsants, such as levetiracetam, pregabalin, tiagabine and zonisamide are less commonly used [33].

Botulinum toxin therapy may be recommended for patients with focal dystonia (e.g. cervical, oromandibular dystonia) [1]. This treatment approach is effective and safe due to lack of systemic side effects. In case the treatment is ineffective, or in severe cases of dystonia, surgical methods can be used – intrathecal baclofen injection, deep brain stimulation of the globus pallidus, pallidotomy [1].

Prevention

Medical professionals' awareness of DID is extremely important to prevent this ADR, especially when antipsychotics and metoclopramide are administered. The drug with the lowest risk of DID should be selected.

Conclusion

Modern demographic trends with an increase in life expectancy and aging of the population, an increase in the number of elderly and senile patients with a large number of comorbid diseases, the problem of polypharmacy and the active development of the pharmaceutical market lead to an increased risk of developing drug-induced syndromes and diseases, including ADID and TDID. At the same time, drug-induced movement disorders are often diagnosed quite late due to physicians' unawareness of this ADR.

Increasing the awareness of different medical specialists, especially of neurologists, psychiatrists, general practitioners, of drugs associated with ADID and TDID, will help optimize pharmacotherapy, administer alternative drugs without this ADR or with minimal risk of this ADR, and use of adequate preventive measures aimed at reducing the risk of these movement disorders.

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