Parkinsonism and Related Disorders 20S1 (2014) S108–S112

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Acute and subacute drug-induced movement disorders

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ARTICLE INFO

Keywords:
Drug-induced movement disorders
Parkinsonism
Dyskinesia
Tremor
Acute dystonic reaction
Akathisia
Neuroleptic malignant syndrome
Serotonin syndrome

SUMMARY

Many pharmacological agents may induce a variety of movement disorders, including dystonia, tremor, parkinsonism, myoclonus and dyskinesia, with an acute, subacute or more chronic time course. Motor symptoms may be isolated or part of a more extensive cerebral or systemic condition, such as the neuroleptic malignant syndrome or the serotonin syndrome. Drug-induced movement disorders share a number of features that should make them easy to identify, including a clear temporal relationship between medication initiation and symptom onset, a dose-effect, and, with the exception of tardive syndromes, complete resolution after discontinuation of the offending agent. Diagnosis relies on a thorough medication history. Medications commonly involved include dopamine receptor blockers, antidepressants and anti-epileptics, among many others. Mechanisms underlying drug-induced movement disorders involve blockade, facilitation or imbalance of dopamine, serotonin, noradrenaline and cholinergic neurotransmission in the basal ganglia. The present review focuses on drug-induced movement disorders that typically develop as an acute (hours to days) or subacute (days to weeks) event, including acute dystonic reactions, akathisia, drug-induced parkinsonism, neuroleptic malignant syndrome, serotonin syndrome, parkinsonism-hyperpyrexia syndrome, drug-induced tremor, drug-induced hyperkinesias and movement disorders associated with the use of recreational drugs.

1. Introduction

Shortly after the large-scale use of the first conventional neuroleptic chlorpromazine in schizophrenia by Delay, Deniker and Harl in 1952, a rapidly growing list of "drug-induced extrapyramidal reactions" was reported [1]. Since many other drugs were later associated with various movement disorders, the concept of drug-induced movement disorders (DIMDs) emerged in the early 1970s as a distinct clinical entity [2] and remains a major contributor to adult and pediatric movement disorders worldwide [3–5].

DIMDs can be classified according to (1) their temporal profile (acute and occurring within hours to days after exposure; subacute and building up more slowly after days to weeks of exposure; and chronic following long-term therapy with the offending medication) [6], (2) their phenomenology (dystonia, dyskinesia, tremor, parkinsonism, myoclonus, akathisia, tic, chorea) [5], and (3) the pharmacological agent likely involved (typical and atypical neuroleptics and other dopamine receptor blockers (DRBs), antidepressants, anti-epileptics, and many others, including recreational drugs and toxic agents). In general, DIMDs are treatable and tend to respond to the discontinuation of the offending agent.

In this paper, the focus is on acute and subacute DIMDs, excluding tardive syndromes (TDs) which are discussed in another review in this supplement [Aquino and Lang, p. S113]. This group of conditions is relatively common yet likely underdiagnosed, since they are usually seen in the emergency room [7–9], and may appear atypical to non-neurologists. Diagnosis and treatment may therefore be delayed and the condition may worsen, whereas early recognition and adequate management leads to usually complete recovery. It is worthwhile to remember that, when facing an acute or subacute movement disorder, DIMD should be high on the list of differential diagnoses, and an extensive medication history is mandatory.

2. Acute dystonic reactions

The prevalence of acute dystonic reactions (ADRs) has been variably estimated to range from 2.3% to 60% of patients treated with conventional neuroleptics [10] and 2% to 3% with atypical ones [11]. Mostly seen after exposure to DRBs, including antiemetics and gastrointestinal promotility agents, ADRs have also been reported after as diverse medications as SSRIs, opioids, methylphenidate, rivastigmine, albendazole, gabapentine, cetirizine, foscarnet, quininine, and during or shortly after general anesthesia using propofol, fentanyl [12], sevoflurane and morphine. Typically, ADRs occur in young males (including adolescents and children), who have a recent history of psychosis for which a high dose DRB has been initiated.

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1353-8020/$ – see front matter

ADRs characteristically start within hours to a few days after a neuroleptic has been introduced, with 50% of cases occurring during the first 24 hours and 90% within the first five days. Clinical manifestations are usually restricted to the head and neck, but, particularly when the medication is maintained, may extend toward upper and lower limbs as well as the trunk. Motor symptoms may be preceded by generalised discomfort, anxiety and restlessness. One of the most common manifestations is acute oro-mandibular dystonia affecting tongue and mouth, impairing speech and sometimes swallowing, potentially leading to temporo-mandibular joint subluxation, and sometimes evolving into overt trismus. Other modes of presentation include oculogyric crises, blepharospasm, complex cervical dystonia with a mixture of retrocollis, laterocollis and antecollis, focal limb dystonia, usually more distal than proximal, Pisa syndrome, and back arching potentially evolving into opisthotonos. A particularly spectacular and life-threatening form of ADR is acute laryngeal dystonia, affecting the vocal cords and laryngeal muscles and leading to upper airway partial or complete obstruction. This condition manifests as stridor, respiratory distress and sudden death. Known since the early use of DRBs [13], electromyography studies have demonstrated overactivity in vocal cord adductors, amenable to botulinum toxin injections in thyroarytenoid muscles with an excellent response [14]. This approach is probably life-saving in some cases.

ADRs respond dramatically, usually within minutes, to intravenous or intramuscular injections of anticholinergic drugs. Depending on the availability of specific medications in individual countries, the following agents may be used: biperiden (2.5–5 mg), procyclidine (5–10 mg), benztropine (1–2 mg), trihexyphenidyl (2.5–5 mg) or diphenhydramine (25–50 mg). Benzodiazepines may also be helpful but are not as effective as anticholinergics. Because of their short half-life, recurrence of the ADR hours after the first anticholinergic injection may necessitate repeated injections and a limited oral course of anticholinergics is usually recommended for a few days. Medications implicated in ADRs, notably DRBs, should be discontinued, although this may not be possible because of an ongoing psychiatric condition. In this case, it has to be kept in mind that patients who have experienced a single episode of ADR are at higher risk for future dystonic reactions when exposed to other DRBs and it is worth discussing a prophylactic approach using low-dose oral anticholinergics in addition to DRB. Interestingly, a few patients have been reported to exhibit drug-induced oculogyric crises that recurred spontaneously months to years after discontinuation of the offending DRB [15], the reason for which remains unclear.

Pathogenic mechanisms of ADRs are uncertain but may involve dopamine receptor blockade being associated with enhanced dopamine turnover and subsequent dopamine receptor supersensitivity. It may also be that the hypodopaminergic state results in relative cholinergic overactivity and muscarinic receptor supersensitivity. An inhibitory effect of M4 muscarinic receptors on striatal D1 dopamine receptor has also been proposed [15]. The propensity for DRBs to bind sigma opiate receptors has been considered as an alternative mechanism. Finally, there may be some genetic background as the basis of the sensitivity of some patients toward these side effects [3].

3. Akathisia

Akathisia has been variably defined and may develop as an acute or chronic movement disorder, or even a tardive syndrome [16]. It is considered the more frequent extrapyramidal manifestation related to the use of DRBs, and has an incidence ranging from 21% to 75%. Acute akathisia typically develops soon (within a few days), after DRB initiation, during dose escalation, or when switching to a more potent DRB [10]. It has a subjective component, including inner tension, anxiety, irritability, the urge to move and a feeling of jitteriness [1]. There is an objective component, with patients exhibiting global restlessness and increased, semi-purposeful motor activity, including the incapacity to stay still, crossing and uncrossing their legs while sitting, and repetitive, stereotypic movements of the trunk, hands or legs. Importantly, in the setting of psychiatric conditions akathisia may be overlooked and misinterpreted as psychotic agitation, euphoria, anxiety, insomnia, delirium, restless legs syndrome or drug withdrawal. Akathisia is not a benign condition as it is considered by patients as highly unpleasant, interfering negatively with quality of life and potentially leading to violent behaviour and to suicide in severe forms.

Acute akathisia tends to persist with DRB maintenance and abates soon after dose reduction or, more frequently, after DRB discontinuation. Atypical neuroleptics are less prone to induce akathisia and may be considered useful alternatives. However, even in this class of agents, the incidence of akathisia and of extrapyramidal side effects varies considerably from one study to another and it is unclear which of clozapine, risperidone, olanzapine, quetiapine, aripiprazole, ziprasidone or paliperidone is superior with respect to risks of developing akathisia [16]. Anticholinergics, beta-blockers, benzodiazepines, amantadine, mirtazapine, and clonidine as add-on medications have all proven useful to reduce akathisia when conventional or atypical neuroleptics have to be maintained, yet the level of evidence, in the absence of randomized controlled trials for most, is generally low.

Acute akathisia is not limited to the use of DRBs and has also been reported with SSRIs, antiepileptics, and cocaine recreational use. In these conditions, therapeutic strategies are similar.

4. Drug-induced parkinsonism

A parkinsonian syndrome developing over a short period of time (days or weeks to months) is highly suggestive of secondary parkinsonism, notably exposure to medications or toxins, and a neurodegenerative origin is rarely part of the differential diagnosis, perhaps with the exception of rapid-onset dystonia-parkinsonism related to mutations in the ATP1A3 gene. Subacute parkinsonism was recognized early on after the initial use of neuroleptics as one of the most frequent extrapyramidal side effects, with an incidence reaching over 15% of patients using conventional neuroleptics [1]. Nowadays, other medications, in particular calcium-channel blockers, seem to be equally frequent offending agents and, in general, it has been proposed that, despite considerable variations in incidence estimates, ranging from 20% to more than 50%, drug-induced parkinsonism (DIP) is the second most common form of parkinsonism in the elderly after Parkinson's disease (PD).

Typically, and at variance with ADR, DIP is more frequent in elderly female patients, overlapping partly with the age, but not gender, distribution of PD, but otherwise differs from PD in many aspects. DIP manifests as an akinetic-rigid, rather symmetrical parkinsonian syndrome that develops over a period of less than three months in 90% of cases and that responds poorly or not at all to levodopa [17]. Tremor and gait impairment is less common than in PD. In pure DIP, DaTSCAN is normal and parkinsonism resolves completely within months after discontinuation of the offending drug, but it may take up to a year in some cases. However, it is not uncommon to see patients whose DIP exhibits an asymmetrical distribution and who demonstrate reduced tracer binding on DaTSCAN images. This pattern is suggestive of preclinical PD or other forms of degenerative parkinsonism, which might have