The syndrome of motor restlessness—a treatable but under-recognised disorder

The syndrome of motor restlessness, or akathisia, is a movement disorder characterised by an irresistible purposeless urge to move about and, in most cases, a sense of inner tension and agitation. During the attack, patients become extremely restless and are unable to sit or stand still. Rarely, akathisia is confined to the lower limbs and in these cases patients stamp their feet repeatedly or cross and uncross their legs without having the urge to walk. In severe cases the syndrome is associated with emotional distress and suicidal attempts have been reported in some patients. Akathisia may also be accompanied by painful oral and genital sensations. These consist of unpleasant paraesthesiae, burning or lancinating pain that does not respond to analgesic drugs, nonsteroidal anti-inflammatory agents, phenytoin or carbamazepine. The onset of drug-induced akathisia may be acute or the syndrome may develop after months or years of exposure to neuroleptic and antidepressant agents (tardive akathisia).

Akathisia is a relatively common but under-recognised extrapyramidal syndrome. The prevalence of this disorder in the general population is not known. However, it is very common in psychiatric patients, occurring in about 30–40% of patients treated with neuroleptic drugs. The syndrome has also been reported to be the commonest extrapyramidal adverse effect of antidepressants which selectively inhibit serotonin re-uptake, accounting for 45% of all movement disorders associated with these drugs. Interestingly, akathisia due to these drugs tends to occur mostly in younger patients, especially women, whereas dystonia, parkinsonism and tardive dyskinesia are found more frequently in older patients.

Aetiology

In most cases akathisia is drug-induced, although it may rarely occur in untreated patients with idiopathic and postencephalitic parkinsonism and following traumatic brain injury. The commonest drugs which cause akathisia are neuroleptic drugs and serotonin re-uptake inhibitors used for the treatment of depression. Lithium has also been implicated in some cases. The syndrome may complicate treatment with levodopa in parkinsonian patients and has also been reported following the withdrawal of tricyclic antidepressants (box 1).

Akathisia due to neuroleptic medication is by far the most frequently encountered entity. Interestingly, some neuroleptic drugs are more likely to result in akathisia than others. Neuroleptic drugs which block both 5-HT2 and D2 receptors, eg, risperidone, are less likely to result in extrapyramidal adverse effects than those which predominantly act on dopaminergic and adrenergic receptors, such as haloperidol. This effect of risperidone may be due to the selective blockade of 5-HT2 receptors in the limbic system (which explains the antipsychotic effect) and its dopamine agonist action in the basal ganglia. Similarly, despite the structural similarities between chlorpromazine and thioridazine, patients are more likely to develop akathisia on chlorpromazine than on equivalent doses of thioridazine.

Rarely reported causes of akathisia include bilateral prefrontal lobe damage secondary to traumatic brain injury, sudden cessation of cigarette smoking and treatment with electroconvulsive therapy (ECT). Nicotine withdrawal has been implicated in the occurrence of psychomotor agitation in a terminally ill patient with cancer. The symptoms were reversed with the use of nicotine skin patches. However, the association between ECT and akathisia is less clear. Although ECT was reported to have triggered the syndrome in one patient, other authors claimed that it improved drug-resistant akathisia in another subject.

The underlying pathophysiological mechanism of akathisia is thought to be imbalance between the cortical and nigrostriatal dopaminergic innervation in favour of increased functional activity of the mesolimbic and nigrostriatal systems, in particular the nucleus accumbens. A syndrome resembling akathisia occurs following stereotactic lesions of the dopaminergic pathways in the frontal lobes in experimental animals and has also been reported in a patient with acquired traumatic damage of the prefrontal cortex. The association of akathisia with the use of some dopamine agonists and the symptomatic improvement following treatment with monoamine-depleting drugs also lend support to this hypothesis.

Iron deficiency anaemia is frequently seen in patients with neuroleptic-induced tardive akathisia but this association has not been observed consistently in the acute form of the syndrome. The pathophysiological significance of the low serum iron in chronic akathisia is not fully understood. Gold and Lenox have recently reviewed the evidence confirming that neuroleptic drugs mobilise iron from peripheral stores and promote its deposition in the basal ganglia and postulated that the excess iron modifies dopaminergic neurotransmission in the nigrostriatal system by binding preferentially to D2 receptors.

Differential diagnosis

The main conditions which need to be distinguished from akathisia are the restless legs syndrome and anxiety states. In addition, akathisia occurring in patients with Parkinson's disease may also be confused with dyskinesias.

The restless legs syndrome is a disorder of unknown aetiology which occurs in 5% of the healthy adult population. It is particularly common during pregnancy with one in every three women affected. In elderly subjects with sleep disturbances the syndrome accounts

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Box 1

**Drug-induced akathisia**

- neuroleptic agents: some are more likely than others to cause akathisia, eg, haloperidol>risperidone; chlorpromazine>
- serotonin re-uptake inhibitors: akathisia most frequently caused by fluoxetine and paroxetine
- other antidepressants: sudden withdrawal of tricyclic antidepressants, combination of monoamine oxidase inhibitors with fluoxetine or tryptophan
- lithium: akathisia may occur at therapeutic levels

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Diagnostic criteria of the restless leg syndrome

- motor agitation, typically characterised by intense desire to walk or move legs, often accompanied by muscle cramps and/or unpleasant skin sensation
- symptoms worse at rest and improved by movement
- symptoms absent or minimal in the earlier part of the day but worsen in the evening and at night
- a normal neurological examination
- onset in late middle life or old age

Box 2

for 23% of cases. Restless legs syndrome is characterised by muscle discomfort, pain and restlessness. The patient often describes a strange crawling sensation in the calf muscles and occasionally similar symptoms in the upper limbs. These symptoms are relieved by walking (box 2). Unlike akathisia, which ceases during sleep, the restless legs syndrome occurs mostly at night and is sometimes associated with nocturnal myoclonus and muscle cramps. Treatment with dopaminergic drugs results in long-term remission of symptoms. Baclofen (20–40 mg/day) is also effective. The response to these drugs may be used as a therapeutic test to confirm the diagnosis.

The hyperactivity associated with anxiety states is often indistinguishable from akathisia, especially in psychotic patients taking neuroleptic drugs. However, the sympathetic overactivity, eg, excessive sweating, palpitations, hyperventilation, tremulousness and dilated pupils, which is characteristic of anxiety and panic attacks is not seen in patients with akathisia. Akathisia is also difficult to diagnose in patients with bipolar affective disorders treated with antidepressant and other medication as the psychomotor agitation associated with drug-induced akathisia could be confused with spontaneous mania, although akathisia is usually milder and short-lived. In addition, patients with spontaneous mania usually have more severe delusions, hallucinations and bizarre behaviour.

Dyskinesias are a common complication of long-term treatment with antiparkinsonian drugs. In contrast to akathisia, these involuntary movements are often unilateral and occur on the side of the body which is affected by the Parkinson’s disease. When the disease is sufficiently advanced the dyskinesia is usually more pronounced in the more severely affected arm and leg. The oro-facial musculature is usually also affected. As a rule the dyskinesias occur or increase in severity approximately 1–2 hours after each dose of the antiparkinsonian medication but are sometimes less predictable, especially in patients with advanced disease.

Management

Withdrawal of the drug causing akathisia often results in rapid symptomatic relief. However, in some patients symptoms may persist for months after discontinuation of the drug. Dose reduction may be sufficient. It has been suggested that the combination of monoamine oxidase inhibitors with fluoxetine or l-tryptophan is associated with an increased risk of developing akathisia. It is logical, therefore, to avoid co-prescribing these drugs. When these options are not available or ineffective, various treatments may be tried, including anticholinergic agents, β-blockers, benzodiazepines, 5-HT receptor antagonists, and mianserin.

Propranolol has been reported to be effective in the treatment of the syndrome of motor restlessness. In a randomised placebo-controlled study, Alder et al. found a significant clinical improvement by the third to fifth day of treatment with either propranolol (80 mg/day) or benztrpine (6 mg/day). Akathisia associated with the use of serotonin re-uptake inhibitors may be prevented or reduced with the concomitant treatment with alprazolam. Anti-serotonergic drugs may also be useful in the treatment of akathisia. In an open clinical trial, Weiss et al. have shown that cyproheptadine given in a dose of 16 mg/day over four days was effective in all 17 patients treated for neuroleptic-induced akathisia. Lithium-induced akathisia was claimed to be particularly responsive to mianserin. Although low serum iron is commonly associated with neuroleptic-induced tardive akathisia, the value of iron supplements in the patients is doubtful and may even be harmful.

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