CASE REPORT

Neurological adverse effects of methylphenidate may be misdiagnosed as meningoencephalitis

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SUMMARY

We present a case of adverse neurological effects of methylphenidate therapy for attention deficit and hyperactivity disorder (ADHD). A 7-year-old boy presented to the emergency department (ED) having developed ataxic gait, orofacial dyskinesias and choreoathetosis of the limbs. The results of all blood investigations, EEG and CT scan of the head were unremarkable. Subsequently, a detailed history revealed he was being treated for ADHD, being started on methylphenidate in the past 3 months. Discontinuation of methylphenidate led to significant and rapid amelioration of neurological adverse effects.

BACKGROUND

Prevalence studies of attention deficit and hyperactivity disorder (ADHD) in the USA suggest 8% of children aged 4 to 17 years are affected.¹ Guidelines recommend behavioural interventions and pharmacological treatment as first-line management.² Methylphenidate is recommended as first-line pharmacological treatment in most guidelines on the management of ADHD.² A large number of children are treated pharmacologically for ADHD, with prevalence studies from numerous European countries reporting around 1% of all children receive methylphenidate. Prevalence studies from numerous European countries report around 1% of children are treated with methylphenidate for ADHD.³

The widespread use of methylphenidate may lead to increasing reports of rare, severe adverse effects, and clinicians should be aware of the possibility of such presentations. Previously published case reports suggest orofacial dyskinesias and choreoathetosis are rare side effects of methylphenidate treatment. The diagnosis of methylphenidate associated neurological adverse effects is mainly clinical, and early recognition would help in limiting unnecessary investigations, medication and inpatient stay.

CASE PRESENTATION

A 7-year-old boy was brought to the emergency department (ED) by ambulance from school accompanied by his mother. The child had apparently fallen onto the floor from sitting position at school, with slow writhing, involuntary movements of face, neck and back. Consciousness was preserved. The description of these movements were most consistent with a dystonia. No preceding illness was reported.

The boy was afebrile. The heart rate, blood pressure, oxygen saturation and respiratory rate were

within the normal range. He had involuntary movements including facial grimacing and contortions with upward eye gaze. There were choreoathetotic limb movements lasting 10–15 s, resolving spontaneously and recurring two or three times a minute. He had ataxic gait. Throughout these episodes, the patient was oriented and able to communicate. The boy denied having hallucinations. Neurological examination revealed mildly hypertonic lower limbs with brisk reflexes, equivocal plantar reflexes and an absence of clonus. The pupils were equal and reactive. Examination of other systems revealed only a soft systolic murmur on auscultation of the precordium.

The child had a diagnosis of Williams syndrome at 2 years of age. A detailed history revealed that a diagnosis of ADHD had been made by a child psychiatrist 3 months earlier. Therapy with methylphenidate 5 mg twice daily had been initiated, before being doubled to 10 mg twice daily 1 month prior to the presentation. The medication was supervised at home with good compliance, and the family felt an overdose unlikely. Accidental ingestion of other medications was unlikely, with other medications being kept out of reach of the patient. No other medical history was reported.

The social history was unremarkable; the child lived with his parents and the family had emigrated from Lithuania about 3 years previously. He was enrolled in a mainstream school with relatively good speech and language, but mild learning difficulties consistent with Williams syndrome.

INVESTIGATIONS

An arterial blood gas was unremarkable. The only abnormality identified on routine page 1 of 5 haematological and biochemical blood testing, was mild hypercalcaemia (2.71 mmol/L), consistent with Williams syndrome. No abnormality was identified on CT scan of the head. EEG did not show any waveforms suggestive of seizure activity or encephalitis.

DIFFERENTIAL DIAGNOSIS

A presumptive diagnosis of meningoencephalitis had been made by the attending doctor in the ED. Intravenous ceftriaxone and acyclovir were administered in the ED. Meningoencephalitis was considered due to the acute change in behaviour and involuntary movements, despite the absence of fever or alteration in sensorium. Subsequently, the child was assessed by the paediatricians as an inpatient. Given introduction of methylphenidate in the past 3 months, an adverse effect from this dopaminergic medication was considered.

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TREATMENT

The child was admitted for 36 h with regular observations and reassessment. Lumbar puncture was not performed as an adverse effect of methylphenidate was considered a more likely diagnosis than meningoencephalitis. Methylphenidate and antibiotics were withdrawn. No specific medication was instituted to treat the neurological symptoms.

OUTCOME AND FOLLOW-UP

The symptoms were found to wane over time. Within 24 h of onset, the orofacial dyskinesias and choreoathetoid movements of the trunk were occurring once or twice a minute but with reduced intensity. At 36 h the boy was significantly better and discharged. A telephone review 1 week later revealed that the boy was doing well with no residual neurological symptoms. He was followed up in the Community Paediatric outpatients and an alternative medication for ADHD was initiated. The publishers of the British National Formulary for Children were informed about this neurological adverse effect of methylphenidate.

DISCUSSION

Methylphenidate is a central nervous system stimulant structurally related to amphetamines. The therapeutic effects are related to the increase in dopamine levels in the central nervous system. Methylphenidate acts by preventing reuptake of released dopamine without effects on the release of dopamine itself.⁴

While an association between methylphenidate and tics is well documented, few case reports exist in the literature reporting methylphenidate-associated orofacial dyskinesias or choreoathetosis.

The European Medicines Agency lists choreoathetoid movements as a very rare side effect of methylphenidate.⁵ Review of the literature identified five cases of methylphenidate-associated choreoathetoid movements, three in adults^{6–8} and two in children.^{9–10} Orofacial dyskinesias are also rarely reported, with nine case reports in the literature including two adults^{7–8} and seven children.^{11–16}

Altogether, 12 cases of methylphenidate-associated orofacial dyskinesia or choreoathetoid movements were identified, of which three were adults and nine children.

Of the nine children, seven had neurological or psychiatric comorbidities,^{10–12–16} including seizure disorders (4/10) and developmental delay (4/10). Five of these children^{10–12–15–16} were taking concurrent antiepileptics or neuroleptics including valproate (3/10), phenobarbital (1/10) or thioridazine (1/10).

All of the three adults had comorbid neurological or psychiatric disorders, including either Parkinson's disease,⁶ bipolar disorder⁷ or acute psychosis.⁸ Preceding the onset of choreoathetosis or orofacial dyskinesia, these three adult patients were administered drugs affecting the central nervous system (levodopa, haloperidol and amobarbital, respectively).

As such, psychiatric and neurological comorbidities were identified as a risk factor for methylphenidate-associated orofacial dyskinesia and choreoathetosis. Concurrent treatment with medication acting on the central nervous system may be a risk factor. The use of these medications as a risk factor for methylphenidate-associated orofacial dyskinesias and choreoathetosis may not exist independently of the relevant comorbidity the medication is treating. Risk factor may not exist independently of the relevant comorbidity the medication is treating.

Notably, these methylphenidate-associated adverse events do not represent overdoses. Doses administered in these cases were within normal therapeutic doses of methylphenidate as per the

American Association of Family Practice guidelines, up to 0.8 mg/kg/day.

Previous authors have identified two categories of movement disorders related to methylphenidate.^{14–16} The first category of methylphenidate-associated movement disorders are characterised by onset immediately following drug introduction. These are associated with rapid onset of symptoms on introduction of methylphenidate, and rapid resolution when methylphenidate is discontinued. These movement disorders are hypothesised to reflect high serum concentrations of methylphenidate, with the duration of symptoms reflecting high levels of the drug in serum.¹⁴ However, experimental evidence of high serum methylphenidate levels during methylphenidate-associated movement disorders is lacking. Methylphenidate levels are not routinely monitored in the clinical setting, and are not available in most hospitals. The main role for methylphenidate drug monitoring is in research and forensic investigations.¹⁷ In this case, methylphenidate drug levels were considered, but the turnaround time for this specialist test made it unsuitable for guiding immediate management.

Seven of the 12 cases fit into this first category, developing rapid onset movement disorders within 1 day of therapy initiation.^{6–8–10–13–16} In the six cases that documented symptom resolution, all resolved completely within 2 days of therapy discontinuation.^{8–10–13–16}

The second category of methylphenidate-associated movement disorders are characterised by symptom onset after several weeks of therapy. The symptoms of this group are thought to continue long after discontinuation of therapy. Sensitivity of the basal ganglia to dopamine has been hypothesised to account for the side effects in this group of patients.^{14–16} Indeed, some of these patients had comorbidities and were on medications such as levodopa, which could have altered the dopamine sensitivity or levels in the basal ganglia.

The remaining 5 of the 12 cases listed above showed onset of movement disorder a few days after therapy initiation.^{7–9–12–14–15} Outcome information is available for four of these cases. In two of the cases, symptoms continued after therapy discontinuation for 2 weeks⁹ and 12 weeks,¹⁵ respectively. Two other cases of these movement disorders were associated with dose increases in the past 1 day, and symptoms ceased after therapy was stopped.^{12–14} The variable off-set of symptoms in these cases and the relation to dose increases suggests the two categories of methylphenidate-associated movement disorders can coexist or overlap.

Learning points

- ▶ The importance of good history taking and examination cannot be underestimated, and may prevent potentially harmful investigations.
- ▶ Orofacial dyskinesia and choreoathetosis are very rare neurological adverse effects of methylphenidate. Widespread use of methylphenidate may mean these adverse effects are seen more frequently.
- ▶ Neurological adverse effects may occur at recommended doses.
- ▶ Risk factors for these adverse effects include comorbid neurological or psychiatric illness and concurrent therapy with anticonvulsants or neuroleptics.
- ▶ Discontinuing methylphenidate therapy may lead to rapid amelioration of neurological side effects.

The evidence suggests the possibility of unmasking of basal ganglia sensitivity, when methylphenidate serum levels rise above a certain threshold.

The characteristics of the 7-year-old boy described in this case report fall within the second category of methylphenidate-associated movement disorders, hypothesised to be caused by basal ganglia sensitivity. First, this patient's movement disorder developed several weeks after the therapy was initiated. The time noted for complete resolution was longer than would be expected if side effects were only due to toxic levels of methylphenidate in serum; the half-life of the drug is known to be less than 12 h. Furthermore, evidence from neuroimaging suggests that Williams syndrome is associated with basal ganglia atrophy.^{18 19}

Contributors LBS and DB were involved in managing the patient, researching the case, acquiring consent and writing the article.

Competing interests None declared.

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