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CASE REPORT

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Reversible cerebral vasoconstriction syndrome in a methylphenidate-treated patient: a case report

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Abstract

Background Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches, often thunderclap headaches, and a multifocal constriction of the cerebral arteries. Although RCVS can occur spontaneously, some cases occur after exposure to drugs. We describe the first case of RCVS in which methylphenidate, a drug with vasoconstrictive properties, is the only suspected drug. Still an unexpected adverse drug reaction of methylphenidate, and so far observed with the concomitant use of vasoactive drugs and methylphenidate, RCVS can be observed when methylphenidate is used alone.

Case presentation A 44-year-old French female presented with sudden onset of severe thunderclap headache during exercise. She had been treated for about 2 years with 54 mg extended-release MPH twice a week for attention deficit / hyperactivity disorder. After clinical, biological and imaging examinations, clinicians concluded to a highly probable RCVS diagnosis, probably linked to methylphenidate use. Major causes of RCVS were ruled out and the methylphenidate treatment was discontinued. The outcome was favourable with nimodipine treatment. We also describe two other cases of methylphenidate induced RCVS recorded in French Pharmacovigilance Database. Moreover, RCVS is an adverse reaction reported more frequently than expected with methylphenidate in the International Pharmacovigilance Database (VigiBase®), suggesting a pharmacovigilance signal. Given its pharmacodynamics, i.e. pre-synaptic dopamine and norepinephrine reuptake inhibition, methylphenidate is theoretically likely to contribute to this vascular event.

Conclusions The role of methylphenidate needs to be considered in case of RCVS diagnosis observed in a treated patient. Although the frequency of this potential adverse drug reaction is expected to be rare, clinicians should be aware of its possible occurrence, given the ever-increasing use of methylphenidate.

Keywords Methylphenidate, Reversible cerebral vasoconstriction syndrome, Pharmacovigilance, Drug safety

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Background

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches, often thunderclap headaches, with or without focal deficit and seizures, and a multifocal constriction of the cerebral arteries, which usually resolves spontaneously within 3 months [1, 2]. Although RCVS can occur spontaneously, especially among middle-aged women, many cases occur after exposure to vasoactive drugs or during the post-partum period [1]. We report here the case of a woman treated with methylphenidate (MPH): she presented at the hospital with thunderclap headache and was diagnosed with RCVS. MPH exposure was identified as a potential trigger for RCVS. Cerebral vasculitis, headaches and tension headaches are expected adverse drug reactions (ADRs) to MPH. However, despite a risk of vasoconstriction reported with MPH alone or in combination with vasoactive drugs [3, 4], RCVS is not part of its safety profile [4]. To the best of our knowledge, the case of RCVS presented here is the first published in which MPH is the only suspected drug. Our patient was not treated with any other known RCVS-inducing drug.

Case presentation

We describe the case of a 44-year-old female patient with ADHD (Attention Deficit / Hyperactivity Disorder). She was treated for about 2 years with 54 mg extended-release MPH twice a week, following the indication for adults as detailed in the Summary of Product Characteristics (SPC) of MPH. She had no other treatment, apart from a copper intrauterine contraception device. Notable events in the patient's history were exercise-induced asthma and heart murmur, with a normal cardiac ultrasound and a normal stress test 6 years earlier. She had no history of migraine.

Three days after the last dose of MPH, while the patient was engaged in intense physical activity, she experienced a sudden severe thunderclap headache with nausea but no vomiting. The patient reported no associated neurological signs. She self-medicated with acetaminophen, which provided a transient improvement in the pain. When she experienced progressive and intense recurrence of her headaches, she presented to hospital. On admission, she had no arterial hypertension. The headache subsided under nefopam. A cerebral angioscan showed no intracranial haemorrhage. No lumbar puncture (LP) was performed. A modally-distributed Willis polygon of regular calibre was found, with no strong argument for RCVS (Fig. 1). However, RCVS diagnosis was envisaged because of the sudden onset of the headache during exercise. The patient reported no use of illicit drugs, cannabis or nasal decongestants. Other clinical and biological examinations were normal. The MPH treatment was discontinued. The patient was discharged on the same day, and was prescribed treatment for RCVS in the form of 30 mg nimodipine 4 times daily for one

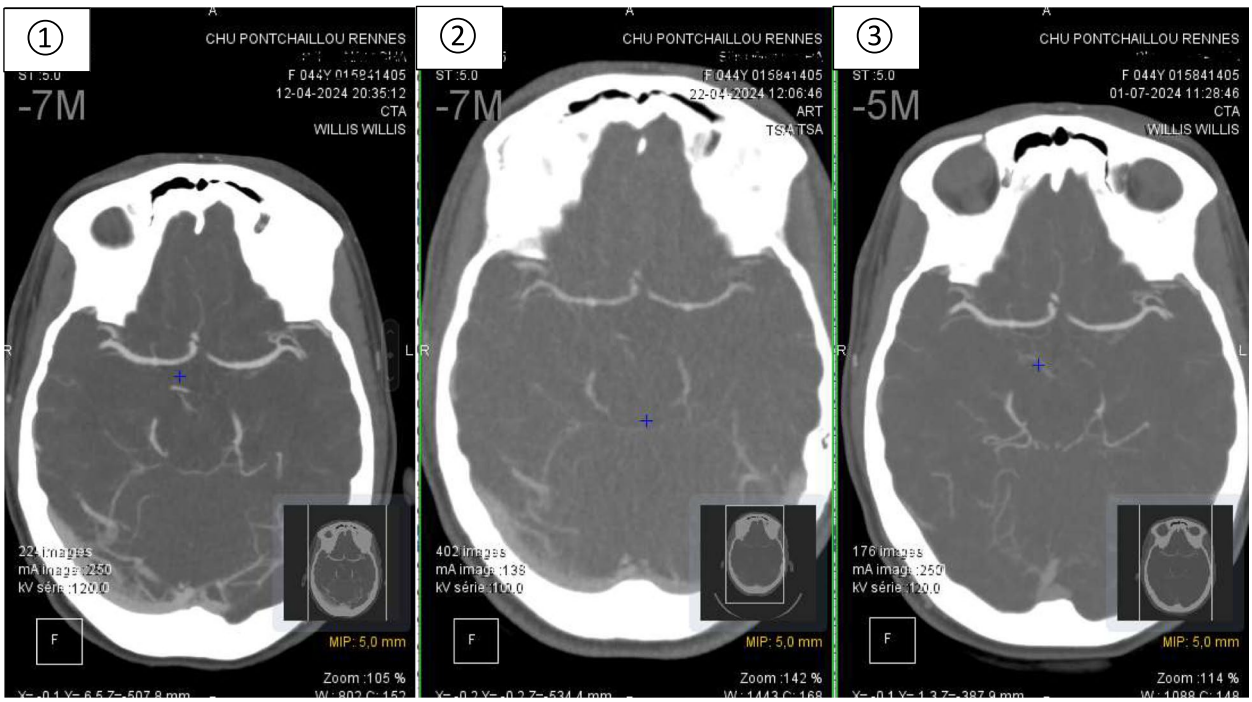

Fig. 1 Imaging results. ① first cerebral angioscan; ② first follow-up angioscan; ③ second follow-up angioscan

month, tapering off thereafter. A contraindication to sport and 3 weeks off work were prescribed. A follow-up angioscan performed ten days after the first one showed a fairly diffuse change in the arterial calibre, tending towards a decrease without significant stenosis, compatible with RCVS (Fig. 1).

After this hospitalization, the evolution of the headaches was favourable, but with a painful background. Initially, the headaches intensified slightly, when climbing stairs for instance. A neurology consultation carried out one month after her hospital stay yielded normal results. No LP was performed at this stage, because of the favourable evolution of symptoms. The clinician concluded to a highly probable RCVS diagnosis, probably linked to MPH use. On the basis of imagery and questions put to the patient, other major causes of RCVS were ruled out, these being post-partum, catecholamine-secreting tumour (no high blood pressure), vasoactive drugs, immunosuppressants or blood products, dissection of cervical arteries (no dissection on angioscan) or even hypercalcaemia, porphyria, head trauma, neurosurgery, subdural spinal haematoma, carotid endarterectomy, cerebral venous thrombosis, CSF hypotension, autonomic dysreflexia and phenytoin intoxication [1]. It should be noted that calcium levels were not measured, but at a subsequent medical consultation the patient showed no signs of hypercalcaemia. Finally, a follow-up angioscan performed 2.5 months after her hospital stay found that the previously visible disparities in arterial calibre had regressed without any significant change in the Willis polygon (Fig. 1). Registered on the French pharmacovigilance database for inclusion in the national and international pharmacovigilance data, the case was also reported as a potential pharmacovigilance signal to the French Medicines Agency.

Discussion and conclusions

At therapeutic doses, MPH can cause headaches and migraine [4, 5]. MPH-induced cerebrovascular disorders, such as cerebral vasculitis or arteritis, cerebral haemorrhage, stroke and cerebral occlusion, have been reported [4–7]. However RCVS is an unexpected ADR of MPH [4].

Firstly, RCVS has been described from the beginning of the 2010s, if a drug aetiology is suspected, the drugs liable to be incriminated are vasoactive drugs including antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin–noradrenaline reuptake inhibitors), α-sympathomimetics (norepinephrine and nasal decongestants such as phenylpropanolamine, pseudoephedrine, ephedrine…), triptans, ergot alkaloid derivatives and illicit drugs (cannabis, cocaine, amphetamines…), but not to the use of MPH, which is a derivative of piperidine, structurally similar to amphetamine [1]. However, in a systematic review in 2021, the authors identified MPH among the drugs that induced RCVS, but unfortunately no detail was provided [8].

We searched the Medline literature database through PubMed using the keywords 'methylphenidate' and 'reversible cerebral vasoconstriction syndrome'. We identified a single case of RCVS in a 16-year-old girl treated with sertraline, a SSRI, and MPH [9]. Both drugs were suspected of causing RCVS and were discontinued, and she was treated with nifedipine. The clinical outcome was rapidly favourable. We did not identify any cases in which MPH was the only drug suspected of causing RCVS.

On July 23, 2024 we searched the French pharmacovigilance database for other cases of RCVS where MPH was the only suspected drug. We used the Preferred Term (PT) "Reversible cerebral vasoconstriction syndrome" from the MedDRA classification for this search [10]. Two other well-documented cases were identified.

The first one involved a 17-year-old girl admitted to hospital for two episodes of sudden headaches with no arterial or venous abnormalities (CT angiography of the intracranial and supra-aortic trunks, MRI and MRI angiography, transcranial doppler). The patient was not receiving contraception. The LP was normal. A RCVS diagnosis was suspected. The patient had been treated for approximately 6 months with MPH at 36 mg/day for ADHD. No aetiology other than MPH was found to explain the RCVS. MPH was discontinued and a treatment with nimodipine at 120 mg/day was initiated. The clinical course was then favourable.

The second case concerned a 32-year-old female patient treated with MPH for concentration disorders (dosage unknown). One year after MPH was initiated, the patient presented very intense posterior thunderclap headaches and cerebral vasospasms, which are symptoms suggestive of a diagnosis of RCVS, requiring hospitalization. The LP was normal. MPH was discontinued and treatment with nimodipine was introduced (120 mg every 4 h). The outcome was favourable with absence of persistent symptoms, and a follow-up CT angiography showing regularization of the artery calibre and no parenchymal abnormalities.

Overall, this brings to three the number of cases of MPH-induced RCVS (in which MPH is the only suspected drug) reported to the French pharmacovigilance database. It should be noted that the three cases of RCVS in patients treated with MPH that we describe were recorded in different regional pharmacovigilance centres in France, and there may be some variability in the documentation of cases depending on the hospital. Thus, although no LP was performed in our case, a normal LP was found in the other two cases described.

On July 26, 2024, we looked for cases of RCVS associated with MPH recorded in the International pharmacovigilance database (VigiBase®), and we identified a dozen cases. This database automatically performs a statistical analysis (disproportionality analysis) for all ADR-drug combinations, making it possible to estimate whether the ADR is reported more frequently than expected [11]. The disproportionality analysis on cases of RCVS is positive for MPH (positive IC025 value of 1.2, with a signal detection threshold when IC025 > 1), suggesting a pharmacovigilance signal. But at this point, a specific study is needed to assess the association between RCVS and MPH and conclude that RCVS could be a new MPH ADR.

In our patient's case, causes of thunderclap headaches other than MPH were ruled out.

Apart from the fact that MPH was the only suspected drug, a pharmacological argument supports the imputability of MPH [12]. Indeed, the use of vasoactive drugs is recognized as one of the main risk factors for RCVS [1, 8, 13, 14]. Given its pharmacodynamics, i.e. pre-synaptic dopamine and norepinephrine reuptake inhibition, MPH is theoretically likely to contribute to this vascular event. It should be noted that the SPC contraindicates its use in combination with other indirect sympathomimetics, with α-sympathomimetics and with ergot alkaloid derivatives on account of the risk of vasoconstriction and hypertensive crises. The mechanisms of this interaction correspond to the accumulation of the vasoconstrictive effects of the two drugs. In addition, Garcia-Argibay et al. reported that the sympathomimetic actions of MPH could result in an increase in circulating norepinephrine levels, with expected effects on peripheral vascular tone and vasoconstriction [3].

In RCVS, the exact pathophysiology of abrupt-onset headache and of the prolonged but reversible vasoconstriction is not known, but reversible angiographic narrowing suggests an abnormality in the control of cerebrovascular tone [14]. We hypothesize that the risk of vasoconstriction reported with MPH alone or in combination with vasoactive drugs could warrant suspicion about its role in the occurrence of RCVS.

In conclusion, given its pharmacodynamics, the role of MPH needs to be considered in case of RCVS diagnosis observed in a treated patient. Although the frequency of this potential adverse drug reaction is expected to be rare, clinicians should be aware of its possible occurrence, given the ever-increasing use of MPH [15].

Abbreviations

ADHD	Attention deficit / hyperactivity disorder
ADR	Adverse drug reactions
MPH	Methylphenidate
SSRIs	Selective serotonin reuptake inhibitors
SPC	Summary of Product Characteristics
RCVS	Reversible cerebral vasoconstriction syndrome

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Authors' contributions
MNO, LMS: Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The use of patients' personal and clinical data is authorized by a European Directive that states that pharmacovigilance systems should use all appropriate measures to obtain accurate, verifiable information for the scientific evaluation of suspected adverse reaction reports, including reidentification of records identifying ADRs [16]. MNO, LMS, ALR, AB, EH and EP are members of the regional pharmacovigilance centres, an integral part of the French national pharmacovigilance system under the aegis of the French Medicine Agency ANSM.
Written informed consent was obtained from the patient for publication of this case report.

Competing interests
The authors declare no competing interests.

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