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Case Report

Atomoxetine-induced focal seizures with contralateral hypoperfusion and hyper-CKemia ☆☆☆★

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ABSTRACT

One of the drugs used to treat attention deficit hyperactivity syndrome is atomoxetine. Usually, the drug is well tolerated but in rare cases adverse events may occur. An 18-year-old female under atomoxetine (60 mg/d) since 2 years for attention deficit hyperactivity syndrome since age 13 years, developed sudden onset headache, hemianopia to the right, hypoesthesia of the tongue and right arm, aphasia, and depersonalisation. Blood tests revealed hyper-CK-emia of 2860U/L, cerebral magnetic resonance imaging showed disturbed perfusion on the left temporo-parieto-occipital region, and electroencephalography (EEG) revealed focal slowing and spikes and sharp waves in the same projections. After discontinuation of atomoxetine, symptoms, EEG, and magnetic resonance imaging findings resolved spontaneously within 48 hours. In conclusion, atomoxetine may rarely cause severe side effects such as complex partial seizures with CK-elevation, transient hypoperfusion of the temporal, parietal and occipital lobes, and prolonged reorientation. Atomoxetine should be discontinued if such side effects occur.

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Introduction

Attention deficit hyperactivity syndrome (ADHS) is an increasingly recognized psychiatric abnormality, which is not only

managed by psychotherapy but also favorably responds to drugs such as methylphenidate, amphetamine, clonidine, atomoxetine, or guanfacine [1,2]. Usually, these drugs are well tolerated [1] but in rare cases adverse events, as in the following case, may occur.

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Case presentation

The patient is an 18-year-old Caucasian female, height 170 cm, weight 60 kg, who developed a foreign body feeling in the right eye on the evening prior to admission. On the morning of admission she developed pain of the right eye, observed partial reddening of the right sclera, and experienced blurred vision on the right eye. In the afternoon she additionally developed mild, bilateral frontal headache with left-sided predominance. One hour later, she noted sudden onset hypoesthesia of the tongue and the right upper extremity. In addition, she noted blurred vision only when looking to the right. She experienced depersonalisation, a feeling of alienation, and speech disturbance, such as word-finding difficulties, paraphasias, and perseverations leading to hospitalization.

The previous history was noteworthy for ADHD since age 13 years, which was treated with psychotherapy, methylphenidate during a few months, and atomoxetine 60 mg/d during the last 2 years. After starting atomoxetine, she had lost 11 kg. She had taken atomoxetine regularly during the last weeks except for the day of admission. The history was negative for fever, infection, depression, sleep disorder, migraine, epilepsy, head trauma, meningitis, illicit drugs, alcohol, or HIV. She was regularly drinking less than 1 liter of liquids per day. She had undergone electric muscle stimulation (EMS) therapy during 45 minutes for recreational purposes 4 days prior to admission without side effects.

On admission she was alert but partially disorientated for time and location. She had word-finding disturbances and paraphasias and tendon reflexes were brisk on the lower limbs but the remainder of the neurological exam was normal. Blood pressure was normal. Electrocardiography (ECG) showed sinus rhythm of 98 bpm and QT-prolongation. Blood chemical investigations revealed slight hypokalemia

of 3.2 mmol/ (n, 3.3-5.1 mmol/L) and creatine-kinase (CK) of 2860U/L (n, <145U/L) but was otherwise normal. Brain magnetic resonance imaging (MRI) revealed marked hypoperfusion of the left temporo-parieto-occipital area (Fig. 1). Immediately after the MRI, she reported that hemianopia and sensory disturbances of the tongue and the right arm had resolved. Cerebrospinal fluid investigations were normal. Atomoxetine was discontinued. EEG on hospital day (hd) 2 revealed slowing in the left temporo-parieto-occipital projections and occasional spikes and sharp waves in the same distribution. Shortly before the control MRI on hd2 the patient experienced syncope with cloni of the left upper limb, The control MRI was normal, particularly no perfusion deficit could be documented any longer. Control-EEG did no longer show the previous abnormalities. During the following days hyper-CKemia continuously regressed.

Discussion

Atomoxetine is a phenoxy-propyl-amine derivative and structurally related to the antidepressant fluoxetine [2]. Atomoxetine functions as a selective norepinephrine reuptake inhibitor, which has been approved for the treatment of ADHD in the nonstimulant class of medication [2]. Whether atomoxetine increases the risk of seizures, is controversially discussed. Some studies found an increase of the seizure risk whereas others did not. Generally, the relation between ADHD and epilepsy is bidirectional [3]. ADHD increases seizure risk, while epilepsy patients have an increased prevalence of ADHD [3]. In a study of 20,032 atomoxetine exposures, major toxicity was observed in only 21 cases (0.11%) [4]. Among these, 9 developed seizures (42.9%), 8 tachycardia (38.1%), 6 coma (28.6%), and 1 ventricular arrhythmias (4.8%) [4]. In a

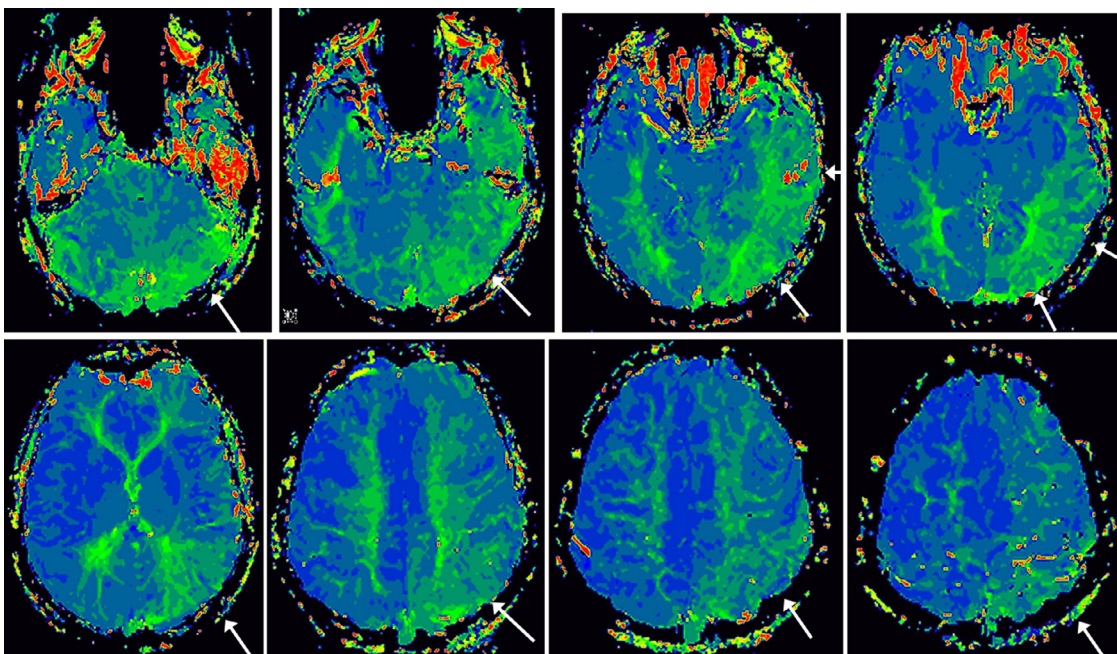


Fig. 1 – Cerebral MRI, perfusion weighted imaging showing diffuse hypoperfusion in the left temporo-parieto-occipital area.

study comparing 13,398 pediatric patients under atomoxetine and 13,322 initiators of stimulants, atomoxetine therapy was not associated with an increased risk of seizures [5]. In a retrospective cohort study of 34,727 patients, there was also no significant association between the use of atomoxetine and seizure risk in ADHS children aged 6-17 years [6]. In a study of 27 patients with epilepsy and treated with atomoxetine, no safety problems were reported [7]. In a series of 40 patients with atomoxetine poisoning only one child developed seizures [8]. Although patients with ADHS have an increased risk of seizures, treatment of ADHS with atomoxetine does not appear to further increase this risk [9]. Whether chronic exsiccosis and the low body weight caused a relative overdose and thus atomoxetine toxicity, remains speculative.

The cause of CK-elevation in the presented patient remains speculative. Definitely excluded were ischemic stroke and myocardial infarction. A possible cause could be a seizure but neither the patient nor her relatives reported one prior to admission. Arguments for a seizure, however, are that she had a sudden-onset symptomatology, that she was found in a confusional state, that her neurological deficits disappeared within a few hours, that EEG showed focal paroxysmal activity, and that she experienced a witnessed seizure on hd2. Arguments against seizures are that the individual/family history was negative for epilepsy, that no triggers, except atomoxetine, of a seizure were noted, and that there was no tongue bite or secessus. Another explanation of CK-elevation could be the EMS 4 days prior to the event. In single patients EMS may cause hyper-CK-emia [10]. CK-elevation as a side effect of atomoxetine has not been reported previously.

Though some authors propose that treatment for ADHS does not need to be discontinued when adverse events occur [1], it seems to be advisable in some cases to alter this strategy and discontinue the drug, as in the present case. Since it cannot be excluded that headache, speech disturbance, visual abnormalities, depersonalisation, and QT-prolongation, were adverse events due to the long-term atomoxetine treatment, discontinuation of the drug in the presented case appears justified. Headache, tachycardia, hypoesthesia, paresthesias, QT-prolongation, psychosis, and seizures have been previously reported as side effects of atomoxetine [2,11,12].

Overall, atomoxetine may cause severe side effects such as complex partial seizures, CK-elevation, transient temporary hypoperfusion of the temporal, parietal and occipital lobes, and prolonged reorientation. Atomoxetine should be discontinued when such side effects occur.

Patient consent

The patient consents with the publication in anonymous form.

Author contribution

JF: design, literature search, discussion, first draft, critical comments

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