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Clarithromycin-Associated Carbamazepine Toxicity Presenting as a Posterior Circulation Stroke Mimic

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Abstract

A woman in her 50s with long-standing epilepsy treated with carbamazepine presented with acute dizziness, vertigo, diplopia, tinnitus, lethargy, and unsteadiness while taking clarithromycin for a lower respiratory tract infection. Her general practitioner withheld her statin because of a known clarithromycin interaction, but her carbamazepine was continued at full dose. Hypertension, hypercholesterolaemia, and an extensive smoking history, combined with a CT of the head that did not detect any acute pathology, made a posterior circulation stroke an initial concern. Serum carbamazepine levels were 18.6 mg/L with a sodium level of 122 mmol/L, significantly below the baseline of approximately 130 mmol/L. Carbamazepine was subsequently withheld, hypovolaemia was corrected, and her symptoms resolved within 48 hours. The patient chose to continue her carbamazepine at a lower dose. This case shows how a well-described interaction can produce a convincing stroke mimic, compounded by hyponatraemia. It also shows how admission was an opportunity to review long-term antiepileptic treatments.

Categories: Neurology, Internal Medicine
Keywords: carbamazepine toxicity, drug-drug interactions, epilepsy treatment, stroke, stroke mimic

Introduction

Approximately a quarter of patients assessed for suspected ischaemic stroke were found to have a stroke mimic. In a review of more than 60 studies, the mimic rate was 24.8%, with toxic-metabolic disturbance, peripheral vestibular disorders, and seizures among the most common causes [1]. Many mimics resolve once the underlying cause is treated, making early recognition worthwhile [2].

Posterior circulation stroke is particularly challenging to distinguish from mimics. Vertigo, diplopia, and gait unsteadiness are associated with vestibular disorders and drug toxicity, whereas non-contrast CT is insensitive to early ischaemia in the posterior fossa [3]. In acute vestibular syndrome, a structured bedside oculomotor examination, known as the head impulse, nystagmus, test of skew (HINTS), performed by trained clinicians outperformed early diffusion-weighted MRI in a prospective study [4].

Carbamazepine has a narrow therapeutic range and is primarily metabolised by CYP3A4. Macrolide antibiotics that inhibit CYP3A4 reduce its clearance [5,6]. Clarithromycin has repeatedly been reported to raise carbamazepine concentrations and cause dizziness, drowsiness, diplopia, as well as ataxia [7-10]. Carbamazepine also causes hyponatraemia, which is more likely to occur at higher serum concentrations and produces similar symptoms [11-13].

The interaction is not new. This case adds three points that are emphasised less often. Firstly, toxicity was mistaken for a posterior circulation stroke in a patient with several vascular risk factors. The risks of adding new medications in patients with polypharmacy, particularly the potential for overlooked drug-drug interactions, were prudent here. Though a different clarithromycin interaction with her statin was recognised and acted on at the time of prescribing, the carbamazepine interaction was overlooked. Finally, hyponatraemia from more than one mechanism added to her symptoms and to the diagnostic uncertainty. Consequently, the episode prompted a shared decision to lower her long-term carbamazepine dose after more than 30 years without seizures.

Case Presentation

A woman in her 50s presented to the emergency department with a two-week history of lethargy, dizziness, rotatory vertigo, tinnitus, new double vision, and unsteady gait. She developed a flu-like illness with a dry cough a few weeks earlier. Within 10 days before presentation, her general practitioner diagnosed a lower respiratory tract infection and subsequently started clarithromycin 500 mg twice daily, which she was still taking when she initially presented. Her neurological symptoms began two to three days after starting clarithromycin. She was advised to withhold atorvastatin during the course of clarithromycin because of the

known interaction. Carbamazepine was continued at her usual dose. She reported reduced oral intake and nausea during illness. She denied fever, productive cough, weight loss, diarrhoea, urinary symptoms, or recent travel.

She had epilepsy for over 30 years; however, she had been seizure-free for decades on carbamazepine 400 mg twice daily. She had previously taken sodium valproate. Her other medical history included hypertension, hypercholesterolaemia, hypothyroidism, previous vertigo, thrombocytosis, and a non-united fracture of the right humerus with residual right-arm weakness. The remainder of her regular medications included ramipril (2.5 mg) once daily, atorvastatin (20 mg at night), levothyroxine (50 µg) once daily, and calcium with vitamin D. The patient was allergic to penicillin. She smoked 10-15 cigarettes per day, with a smoking history of greater than 30 years, and drank little alcohol. The patient was independent in her activities of daily living.

Upon examination, she was alert and clinically dehydrated. Her observations were as follows: blood pressure 110/70 mmHg, heart rate 75 bpm, and oxygen saturation 98% on room air; she was apyrexial. She had diplopia on right lateral gaze. There was a long-standing bilateral tremor, more pronounced on intention. Apart from chronic right-arm weakness, there were no focal motor or sensory deficits. The patient was unsteady while walking. Chest and cardiovascular examinations were unremarkable.

Investigations

CT of the head showed no acute intracranial abnormalities (Figure *1*). Serum carbamazepine was 18.6 mg/L (local reference range: 4-12 mg/L). Serum sodium was 122 mmol/L, which was significantly lower than the previous baseline of approximately 130 mmol/L. Urine sodium was 72 mmol/L, and urine osmolality was 328 mOsm/kg. Thyroid function, 9 am cortisol (324 nmol/L), calcium (2.46 mmol/L), and magnesium levels were normal. Haemoglobin was 128 g/L, estimated glomerular filtration rate was above 90 mL/min/1.73 m^2, and C-reactive protein level was 3 mg/L. *Legionella* and pneumococcal urinary antigen test results were negative. Chest radiography was also performed and was normal. The electrocardiogram (ECG) showed sinus rhythm with an RSR′ pattern and ST deviation in lead V2 only with a normal QTc. Table *1* presents the key results.



FIGURE 1: Non-contrast CT of the head at presentation showing no acute intracranial abnormality

Investigation	At presentation	Day 4 after discharge	Reference range
Blood tests			
Serum sodium (mmol/L)	122	132	133-146
Serum carbamazepine (mg/L)	18.6	11.4	4-12
Haemoglobin (g/L)	128	-	115-165
eGFR (mL/min/1.73 m²)	>90	-	>90
C-reactive protein (mg/L)	3	-	<5
Adjusted calcium (mmol/L)	2.46	-	2.20-2.60
Magnesium (mmol/L)	Normal	-	0.70-1.00
Thyroid function	Normal	-	TSH 0.27-4.20 mU/L; free T4 12-22 pmol/L
9 am cortisol (nmol/L)	324	-	133-537
Urine tests			
Urine sodium (mmol/L)	72	-	No fixed range; >30 in hyponatraemia suggests renal sodium loss
Urine osmolality (mOsm/kg)	328	-	50-1200; >100 in hyponatraemia indicates impaired water excretion
Legionella urinary antigen	Negative	-	Negative
Pneumococcal urinary antigen	Negative	-	Negative
Imaging and electrocardiogram			
CT of the head (non-contrast)	No acute intracranial abnormality (Figure 1)	-	-
Chest radiograph	Normal	-	-
Electrocardiogram	Sinus rhythm; RSR' pattern; ST deviation in lead V2 only; normal QTc	-	-

TABLE 1: Results and investigations

eGFR: estimated glomerular filtration rate; TSH: thyroid-stimulating hormone

Differential diagnosis

Posterior circulation ischaemia was the primary concern because of the abrupt onset of vertigo, diplopia, and imbalance in a smoker with hypertension and hypercholesterolaemia. A normal CT did not exclude it [3]. Features that cast doubt over posterior circulation stroke were the absence of a new focal deficit, an interacting antibiotic taken up to the day of presentation, a supratherapeutic carbamazepine level, and complete resolution within 48 hours of withholding carbamazepine. Neurology reviewed her and did not advise MRI, given the rapid recovery and clear alternative explanations.

Carbamazepine toxicity was the most likely single explanation. Dizziness, diplopia, nystagmus, and ataxia

are its typical features [14,15]; the level was raised, and symptoms began when she was taking both drugs [9,10].

Hyponatraemia was a second contributor. The sodium level of 122 mmol/L was well below the usual value. Hyponatraemia with carbamazepine is associated with dizziness, tiredness, unsteadiness, and diplopia [13].

Vestibular neuritis or labyrinthitis was considered because of the preceding viral illness, vertigo, and tinnitus but did not account for the drug level, lethargy, or the hyponatraemia. A seizure or postictal state was considered, given her epilepsy, but there was no witnessed seizure activity.

Treatment

Carbamazepine was withheld on admission. Seizure precautions were put in place, with a plan to administer levetiracetam if seizures occurred, and neurology advice was sought. Clarithromycin was stopped, and ramipril was withheld.

She was clinically hypovolaemic after several days of infection, nausea, and poor oral intake; therefore, she received intravenous 1 L of 0.9% sodium chloride over 12 hours with serial sodium measurements to avoid overly rapid correction. Isotonic saline was used to restore circulating volume. Fluid restriction, the usual first step for carbamazepine-related antidiuresis, would have been inappropriate since the patient was fluid-depleted.

After discussion with neurology, carbamazepine was restarted at 300 mg twice daily. The options discussed with her were continuing at 300 mg twice daily, returning to 400 mg twice daily, or a slow withdrawal given more than 30 years without seizures. She did not drive and chose to stay at a dose of 300 mg twice daily. The patient was discharged after two days with a same-day emergency care review the following week.

Outcome and follow-up

At review in the ambulatory clinic (same-day emergency care) on day 4 post-discharge, sodium was 132 mmol/L and carbamazepine 11.4 mg/L, and she had no seizures. Dizziness, vertigo, and diplopia resolved within 48 hours of carbamazepine withdrawal.

She reported shaking of the limbs and head, which was most noticeable on the stairs and when using her hands. She had experienced similar symptoms for a few weeks after discontinuing valproate several years earlier. Neurology advised that this did not sound like seizure activity and may be related to dose changes. The plan was to continue carbamazepine 300 mg twice daily, record any further episodes on video, and ask her general practitioner to review her long-standing tinnitus.

Discussion

This presentation had features that should prompt concern about posterior circulation stroke: sudden vertigo, diplopia, and imbalance in someone with several vascular risk factors, where a normal CT provides little reassurance [3]. The medication history changed the diagnosis. She was taking clarithromycin alongside full-dose carbamazepine, her carbamazepine level was approximately 50% above the upper end of the usual range [15], and she recovered within two days of the drug being withheld.

This interaction has been recognised since the early 1990s. Albani et al. described an increase in carbamazepine concentration during a 10-day clarithromycin course despite dose reduction [7]. O'Connor and Fris found that levels rose in five patients even after pre-emptive dose reductions of 30-40% and three developed toxic levels. They advised avoiding clarithromycin where possible or reducing the carbamazepine dose by 30-50% with close monitoring if it must be used [8]. In seven psychiatric inpatients given a five-day course, four developed drowsiness, dizziness, or ataxia, with carbamazepine concentrations roughly double those measured after the antibiotic was stopped. Symptoms settled within five days of clarithromycin discontinuation [9]. A French series reported levels of 13.3-28.5 mg/L with ataxia, dizziness, and diplopia [10], and our patient's level falls within that range. The mechanism involves the inhibition of CYP3A4-mediated carbamazepine metabolism [5,6]. Her timeline fits this literature, with symptoms developing during co-administration.

What makes this case interesting is that the prescriber recognised one clarithromycin interaction, but not the other. Atorvastatin was withheld, which was appropriate, whereas carbamazepine remained unchanged. In patients with a penicillin allergy, clarithromycin is a common choice for lower respiratory tract infections. However, alternatives exist, such as doxycycline or azithromycin, which have little effect on CYP3A4 [6]. When clarithromycin is unavoidable, the literature supports a pre-emptive carbamazepine dose reduction with advice about toxic symptoms [8]. A full review of every interacting drug at the point of prescription, rather than of one flagged interaction, would probably have prevented this admission.

Hyponatraemia most likely had more than one cause. Carbamazepine has an antidiuretic effect, and in a cohort of more than 1,400 people taking it, one-quarter had hyponatraemia [12]. High serum carbamazepine

levels are among the main risk factors [12]. Kanbay et al. reported that hyponatraemia was attributed to the combined effects of carbamazepine and clarithromycin [16]. In our patient, poor intake and nausea during the infection resulted in a hypovolaemic component, and her baseline sodium level was already low. Ramipril may also have contributed and would have raised urinary sodium levels, so urinary sodium studies were interpreted with caution [17]. People with carbamazepine-induced hyponatraemia report dizziness, tiredness, unsteadiness, and diplopia more often than those with normal sodium levels [13]. The interaction may, therefore, have worsened her symptoms in two ways: by raising the drug level directly and by lowering the already reduced sodium.

The toxicity was mild. Most patients improve with supportive care, withdrawal of the interacting drug, a pause or reduction in carbamazepine, and monitoring of neurological status, ECG, and serum levels [18]. Extracorporeal removal is reserved for severe poisoning such as refractory seizures or life-threatening arrhythmia [19]. The episode also created an opportunity to review prescriptions that had not changed over the past decades. After more than 30 years without seizures, she was offered continuation, a lower dose, or gradual withdrawal and subsequently chose the lower dose.

This case had limitations that are acknowledged here. MRI was not performed, on neurology advice, so a small posterior circulation infarct cannot be excluded completely, although a full recovery within 48 hours and the laboratory findings make it unlikely [20]. Structured bedside vestibular and oculomotor tests, including the HINTS examination, were also not documented in this case.

Conclusions

This case shows that clarithromycin-associated carbamazepine toxicity can closely mimic a posterior circulation stroke. A thorough medication history is therefore central to the initial assessment of suspected posterior circulation stroke in patients taking carbamazepine. When clarithromycin is prescribed, every potential interaction should be checked, not only the one flagged at the point of prescribing. For patients taking carbamazepine, an alternative antibiotic should be chosen where possible; if clarithromycin is unavoidable, the carbamazepine dose should be reduced and patients warned about symptoms of toxicity. The central lesson of this case is that, in a patient taking five regular medications, one clarithromycin interaction was recognised at the point of prescribing but another was not. Hyponatraemia in this setting may have multifactorial causes, including the effect of carbamazepine, higher drug levels, and hypovolaemia from intercurrent illness. Fluid management should be guided by the patient's volume status. Clinicians should keep a broad range of differentials when seeing patients of such symptomology on the acute medical take.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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