CASE REPORT

Levetiracetam-induced eosinophilic pneumonia

Aisling Fagan,¹ Jonathan Fuld,¹ Elaine Soon²¹Department of Respiratory Medicine, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK²Department of Medicine, University of Cambridge, Cambridge, UK

Correspondence to

Dr Aisling Fagan,
faganai@tcd.ie

Accepted 21 February 2017

SUMMARY

Levetiracetam is widely regarded as a benign antiepileptic drug, compared to older antiepileptic medication. We report a case of eosinophilic pneumonia due to levetiracetam use in a non-smoking woman aged 59 years with no previous respiratory history. Our patient presented with exertional breathlessness and marked desaturation on exertion. She displayed 'reverse bat-wing' infiltrates on her chest radiograph and peripheral eosinophilia on a complete blood count. Her symptoms, radiology and peripheral eosinophilia resolved completely with cessation of levetiracetam and a course of prednisolone. This is the first report of isolated eosinophilic pneumonia due to levetiracetam. Other reports of levetiracetam-induced eosinophilia describe drug rash, eosinophilia and systemic symptoms (DRESS syndrome). Detection of pulmonary drug reactions requires a careful drug history and high index of suspicion. Identifying and reporting a causative agent is crucially important, as cessation of the drug is essential for resolution of the syndrome.

BACKGROUND

Levetiracetam is a relatively recently introduced antiepileptic drug that functions by binding to synaptic vesicle protein (SV2A), thus reducing the rate of vesicle release.¹ It has been recommended by NICE as an alternative first-line treatment in focal and myoclonic seizures, as well as an adjunctive treatment for focal, generalised tonic clonic and myoclonic seizures.²

Levetiracetam is growing in popularity as it is widely regarded as a benign antiepileptic with comparatively few side effects and interactions, particularly when compared to older drugs such as carbamazepine. For example, levetiracetam is linked to cutaneous reactions in ~1.7% of patients compared to 5–15% for phenytoin, carbamazepine and phenobarbitone and 8.3–20% for lamotrigine.^{3–5} Levetiracetam also appears to have a far lower incidence of the rarer but potentially very dangerous idiosyncratic reactions such as agranulocytosis and aplastic anaemia (carbamazepine and phenytoin), pancreatitis (carbamazepine and phenytoin) and hepatic failure (valproate, carbamazepine and phenytoin). Direct comparisons are difficult as levetiracetam was launched recently, and there are few blinded randomised control trials comparing antiepileptics. This is the first known report of isolated eosinophilic pneumonia secondary to levetiracetam.

CASE PRESENTATION

A non-smoking woman aged 59 years presented with several weeks of exertional breathlessness and night sweats. She had been recently diagnosed with

a meningioma and linked her symptoms to starting levetiracetam 8 weeks prior (as treatment for meningioma-related absence seizures). She did not have a cough, chest pain or any other previous medical history. Her physical examination was unremarkable other than peripheral oxygen saturations, which dropped from 95% to 88% on exercise. There was no wheeze, rash, lymphadenopathy or angioedema.

INVESTIGATIONS

New eosinophilia ($8.38 \times 10^9/L$) was the only abnormality on blood tests. Her chest radiograph (figure 1A) showed 'reverse bat-wing' infiltrates in an asymmetrical pattern (more marked on the right). Computed tomography showed peripheral areas of consolidation (figure 1B).

DIFFERENTIAL DIAGNOSIS

Eosinophilia can be defined as a raised eosinophil count of $\geq 0.5 \times 10^9/L$, with hypereosinophilia indicating severe eosinophilia ($\geq 1.5 \times 10^9/L$) and hyper-eosinophilic syndrome describing hypereosinophilia occurring on at least two occasions with end-organ damage attributable to the eosinophilia. Eosinophilic pneumonias are a heterogeneous group of disorders characterised by eosinophilia and pulmonary infiltrates. In eosinophilic pneumonias, the eosinophilia can affect the peripheral blood and the lungs or be limited to the lungs. Eosinophilic pneumonias can be part of an underlying disorder (such as allergic broncho-pulmonary aspergillosis, autoimmune disorders such as eosinophilic granulomatosis with polyangiitis, infections, particularly of a parasitic nature, and malignancy) or they can primarily affect the lungs (acute eosinophilic pneumonia, chronic eosinophilic pneumonia and drug-induced eosinophilic pneumonia).

Our patient was a life-long resident of the UK with no recent travel history or symptoms to suggest parasitic infection. There was no history of weight loss, lymphadenopathy or any other abnormality in the full blood count (aside from eosinophilia) that would suggest an underlying malignancy. Levetiracetam was the only drug that had been recently started, and our patient denied any over-the-counter medications or herbal supplements. The combination of temporally linked symptoms, eosinophilia and suggestive radiology was felt to be highly characteristic of a drug reaction; therefore, tissue biopsy was not sought.

TREATMENT

Our patient was reasonably well, her eosinophilic pneumonia appeared to be clearly driven by the levetiracetam and she had a good support network

CrossMark

To cite: Fagan A, Fuld J, Soon E. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-219121

Figure 1 (A) Plain chest radiograph of the patient on admission (I), after levetiracetam cessation and 12 days of prednisolone (II) and after levetiracetam cessation and 4 weeks of prednisolone (III). (B) Selected computed tomography slices (performed on initial diagnosis) showing patchy areas of ground-glass throughout the lung fields.

at home. Therefore, we felt that outpatient treatment was appropriate. The levetiracetam was stopped. As she had previously experienced meningioma-related seizures, she was discussed with the neurosurgical team, and phenytoin was prescribed as a replacement antiepileptic. As there was evidence of end-organ dysfunction (in the form of exertional desaturation), she was treated with a course of prednisolone, which was tapered off gradually over the next 2 months.

OUTCOME AND FOLLOW-UP

The patient was followed-up 12 days later. She had clinically improved but still had low-level eosinophilia ($1.28 \times 10^9/L$). One month later, her chest radiograph (figure 1AIII) and eosinophil count (table 1) had normalised and she was symptom-free.

DISCUSSION

The original clinical trials of levetiracetam reported accidental injury, asthenia, dizziness, headache, infection, nausea and somnolence as primary adverse reactions.⁶ Interestingly, none of them occurred more frequently than in placebo arms. Since then, the most commonly reported side effects of levetiracetam are neuropsychiatric (in ~13% of adult patients); ranging from dizziness, somnolence, depression and hostility, to frank psychosis.⁷ This is the first report of 'stand-alone' eosinophilic pneumonia due to levetiracetam. Other reports of levetiracetam-induced eosinophilic syndromes describe drug rash, eosinophilia and systemic symptoms (DRESS syndrome) with concomitant pulmonary infiltrates.^{8–11}

Antiepileptic drugs, in particular carbamazepine, phenytoin and phenobarbital, are the most common causes of drug-induced eosinophilia and DRESS, but allopurinol, antibiotics (especially sulphonamides), antimalarials and nonsteroidal anti-inflammatory drugs have also been implicated.¹² DRESS is a delayed T-cell-mediated reaction and several causes have been proposed, including a genetic deficiency of drug-metabolising enzymes, associations with specific human leucocyte antigens and possible reactivation of latent herpes viruses through drug-virus interactions.¹³ Cross-reactions between phenytoin, carbamazepine, phenobarbitone and oxcarbazepine are common as they share a similar 'aromatic' structure.¹⁴ Levetiracetam has a different structure, which may account for the low incidence of cross-reactivity with other antiepileptics.

Detection of pulmonary drug reactions and DRESS requires a careful history and high index of suspicion. The RegiSCAR scoring system has recently been developed to report and grade suspected DRESS cases as being 'unlikely to be drug-associated', 'possible', 'probable' or 'definite'.¹⁵ Prompt recognition is crucial as the mortality associated with DRESS approaches 10%.¹² Pulmonary drug reactions and DRESS syndrome are managed by withdrawal of the offending agent and careful supportive treatment.¹⁶ Corticosteroids are frequently used but evidence is limited. Helpful resources for information on drug-induced respiratory disease include the Pneumotox website¹⁷ and the U.S. Food and Drug Administration Medwatch programme.¹⁸ The former is particularly user-friendly as it allows searching the database by individual drug

Table 1 Longitudinal charting of peripheral eosinophilia

Timepoint	Baseline	At presentation	After 12 days of prednisolone and levetiracetam cessation	After 4 weeks of prednisolone and levetiracetam cessation
Eosinophil count ($\times 10^9/L$)	0.39	8.38	1.28	0.11

names and by patterns of pulmonary disease. Reporting of drug reactions is critical to allow clinicians a complete view of the risk/benefit balance prior to recommending specific medications.

Learning points

- ▶ New eosinophilia ($>0.5 \times 10^9/L$ or 3% of leucocytes) should always raise the possibility of drug-induced syndromes.
- ▶ Detection of pulmonary drug reactions requires a careful history and high index of suspicion. The physician should enquire not only about prescribed medications but also over-the-counter remedies, herbal supplements and illicit drug use.
- ▶ Identifying and reporting a causative agent is important, as cessation of the agent is crucial for resolution of the pulmonary syndrome.

Contributors JF and ES initially diagnosed and treated the patient. The decision to publish was made between all parties. AF contacted the patient for permission and wrote first draft and subsequent drafts of manuscript. JF and ES reviewed and edited all drafts before submission. Literature review was performed by AF and ES.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Lynch B, Lambeng N, Nocka K, *et al.* The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. *Proc Natl Acad Sci* 2004;101:9861–6.
- 2 Epilepsies: diagnosis and management. Nice.org.uk. 2012. (cited 29 January 2017). <https://www.nice.org.uk/guidance/cg137/chapter/About-this-guideline>
- 3 Błaszczyk B, Lasoń W, Czuczwar S. Antiepileptic drugs and adverse skin reactions: an update. *Pharmacol Rep* 2015;67:426–34.
- 4 Wang XQ, Lang SY, Shi XB, *et al.* Antiepileptic drug-induced skin reactions: a retrospective study and analysis in 3793 Chinese patients with epilepsy. *Clin Neurol Neurosurg* 2012;114:862–5.
- 5 Anderson G. Children versus adults: pharmacokinetic and adverse-effect differences. *Epilepsia* 2002;43(Suppl 3):53–9.
- 6 Welty T, Gidal B, Ficker D, *et al.* Levetiracetam: a different approach to the pharmacotherapy of epilepsy. *Ann Pharmacother* 2002;36:296–304.
- 7 Wade JF, Dang CV, Nelson L, *et al.* Emergent complications of the newer anticonvulsants. *J Emerg Med* 2010;38:231–7.
- 8 Gómez-Zorrilla S, Ferraz A, Pedrós C, *et al.* Levetiracetam-induced drug reaction with eosinophilia and systemic symptoms syndrome. *Ann Pharmacother* 2012;46:e20.
- 9 Flannery A, Willey M, Thompson Bastin M, *et al.* Eosinophilia and fever with levetiracetam: a case report. *Pharmacotherapy* 2015;35:e131–5.
- 10 Dar WR, Sofi N, Latief M, *et al.* Levetiracetam induced drug reaction with eosinophilia and systemic symptom syndrome. *Indian J Dermatol* 2016;61:235.
- 11 Bayram AK, Canpolat M, Çınar SL, *et al.* Drug reaction with eosinophilia and systemic symptoms syndrome induced by levetiracetam in a pediatric patient. *J Emerg Med* 2016;50:e61–6.
- 12 Choudhary S, McLeod M, Torchia D, *et al.* Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. *J Clin Aesthet Dermatol* 2013;6:31.
- 13 Cacoub P, Musette P, Descamps V, *et al.* The DRESS syndrome: a literature review. *Am J Med* 2011;124:588–97.
- 14 Romano A, Pettinato R, Andriolo M, *et al.* Hypersensitivity to aromatic anticonvulsants: in vivo and in vitro cross-reactivity studies. *Curr Pharm Des* 2006;12:3373–81.
- 15 RegiSCAR. Regiscar.org. (cited 29 January 2017). http://www.regiscar.org/Diseases_HSS_DRESS.html
- 16 Tas Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology* 2003;206:353–6.
- 17 Camus P, Foucher P. Pneumotox 'Drug' [Internet]. Pneumotox.com. 1997. (cited 29 January 2017). <http://www.pneumotox.com/>
- 18 MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Fda.gov. (cited 29 January 2017). <http://www.fda.gov/Safety/MedWatch/default.htm>

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow