CASE REPORT

Normoammonemic encephalopathy: solely valproate induced or multiple mechanisms?

Sanjay Budhdeo,¹ Malcolm Marquette,² Deepwant Singh,³ Vivek Rajagopal³¹Cambridge University, Cambridge, UK²Addenbrooke's Hospital, Cambridge, UK³Department of Rheumatology, West Suffolk Hospital, Bury St Edmunds, UK**Correspondence to**

Dr Sanjay Budhdeo, sb930@cam.ac.uk

SB and MM contributed equally to this manuscript.

Accepted 10 February 2014

SUMMARY

A 77-year-old woman presented with subacute onset progressive confusion, aggression, auditory hallucinations and delusions. In the preceding months, the patient had a number of admissions with transient unilateral hemiparesis with facial droop, and had been started on valproate for presumed hemiplegic migraine. Valproate was withdrawn soon after admission and her cognitive abilities have gradually improved over 3 months of follow-up. Valproate levels taken prior to withdrawal were subtherapeutic and the patient was normoammonaemic. EEG undertaken during inpatient stay showed changes consistent with encephalopathy, and low titre *N*-methyl-D-aspartate (NMDA) receptor antibodies were present in this patient. The possible aetiologies of valproate-induced encephalopathy and NMDA receptor-associated encephalitis present a diagnostic dilemma. We present a putative combinatorial hypothesis to explain this patient's symptoms.

BACKGROUND

This case illustrates the importance of a wide differential diagnosis when considering patients with subacute onset confusion. This case also documents a diagnostic dilemma between valproate-induced encephalopathy and autoimmune encephalitis to *N*-methyl-D-aspartate (NMDA) receptors.

CASE PRESENTATION

A 76-year-old woman was initially admitted after subacute onset of confusion, aggression, auditory hallucinations and delusions. The onset of confusion was gradual over a 6-week period prior to admission. At first, the patient noticed difficulty in sending text messages on her mobile telephone, then encountered difficulty in using the remote control for her television and in dialling numbers to make telephone calls. Immediately prior to admission, she had been found wandering outside her house unsure of her location. In the 2 weeks prior to admission, her sister had stayed with her and noted that the patient was uncharacteristically aggressive, with many arguments between them.

Her medical history included type 2 diabetes and hypertension. She has had an episode of expressive dysphasia without facial involvement or limb weakness 4 years prior to this admission, after which she underwent carotid endarterectomy for carotid artery stenosis. She presented again 4 months prior to admission with left-sided headache and expressive aphasia without weakness. Opticians had noted a right homonymous hemianopia but this had resolved by the time of her admission to the

emergency department. Three months prior to admission, she presented to the emergency department with left-sided headache and a sensation of heaviness, no objective weakness, and improved spontaneously. On those admissions, she had multiple CT and MRI (including diffusion weighted sequences) of her head which revealed no abnormalities except background small vessel disease. She had carotid Dopplers which did not show critical obstruction (50%). She was presumed to have had transient ischaemic attacks given her medical history of type 2 diabetes and hypertension and had been placed on medical therapy for primary prevention of stroke as per National Institute for Health and Care Excellence (NICE) guidelines for primary stroke prevention; however, given repeated presentations, alternative diagnoses were considered and she was started on sodium valproate 300 mg once daily for a possible diagnosis of hemiplegic migraine just over 2 months prior to admission. No other changes to medication had been made. Other medication of note was metformin 1 g twice daily for diabetes mellitus, doxazosin 4 mg once daily, lisinopril 20 mg once daily and bisoprolol 2.5 mg once daily for hypertension.

Her change in cognitive state appeared to be temporally associated with starting sodium valproate. The family reported that her symptoms had gradually started in the weeks after valproate was first given, and worsened when the valproate dosage was increased to 600 mg once daily, approximately 1 month prior to admission.

On examination, reflexes were difficult to elicit throughout even with reinforcement. There was no visual field deficit. There was nominal dysphasia, with the patient being unable to name a watch and a pen. The patient had difficulty with praxis and sequencing tasks. On mental state examination, she had predominantly persecutory delusions. At various points during her stay, she thought that her medical team was part of a conspiracy against her, thought that she had been to a sewer overnight and thought that police had visited the hospital in order to take her away. The delusions became less severe over the patient's inpatient stay, and the patient started expressing doubts over the veracity of her thoughts.

INVESTIGATIONS

Prior to stopping valproate, valproate levels were taken from the patient and were shown to be subtherapeutic (21 mg/L). Ammonia levels were normal. Serum NMDA receptor antibodies had a low positive titre of 118 µmol/L. Antibodies to

CrossMark

To cite: Budhdeo S, Marquette M, Singh D, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-201928

voltage-gated potassium channels were negative. There were no positive results from vasculitic screen. Cerebrospinal fluid protein and glucose levels were normal in comparison with serum and there were no oligoclonal bands. There were no cerebrospinal fluid lymphocytes.

There were no new changes on head CT or MRI of the head on this admission. EEG showed diffuse δ wave slowing consistent with encephalopathy.

DIFFERENTIAL DIAGNOSIS

There are a number of causes of subacute confusion beyond the two possibilities considered in the article. Endocrine causes include hypoglycaemia, hypothyroidism, hyponatraemia and other electrolyte abnormalities. Metabolic causes include vitamin B₁₂ deficiency and alcohol withdrawal. Systemic causes include hepatic encephalopathy. Neuroinfectious conditions include HIV. Inflammatory causes include cerebral vasculitis and Hashimoto's encephalopathy. Degenerative causes include prion disease.¹

While valproate encephalopathy presents with neuropsychiatric symptoms described above,² there are more severe presentations which involve loss of consciousness, seizures, fever and focal neurology.³ Similarly, NMDA receptor encephalitis has a more severe presentation involving movement disorders, seizures and hypoventilation.

TREATMENT

The patient's symptoms remitted over the course of months without pharmacological or surgical therapy, such that she is living independently, with frequent contact from family and friends to ensure no ongoing problems. The patient declined further screening to test for malignancy.

OUTCOME AND FOLLOW-UP

ACE-3 on admission was 30/100. On repetition after approximately 5 weeks, it was 68/100. On discharge, the patient first stayed with family so she could build up the confidence to live independently. After a few weeks, she moved back to her home, where she has been managing independently and receives no care.

DISCUSSION

The temporal association of symptoms with valproate administration and amelioration of symptoms with stopping valproate are consistent with previous reports of valproate encephalopathy in the literature.² The period of time taken for symptoms to develop is longer than previously reported⁴; however, this may be owing to the lower dose of valproate involved in this case.

The initial symptoms in this case were more typical of NMDA receptor encephalitis; furthermore, the episodes of transient neurological symptoms that the patient exhibited on previous attendances to the emergency department could also have been consistent with an NMDA receptor-associated encephalopathy. The presentation was, however, atypical in that the patient was older than is normally seen in NMDA receptor encephalitis, there was a spontaneous resolution of symptoms and there was a lack of stage 2 symptoms (such as spontaneous reduction in conscious level, dysautonomia and movement disorder).⁵

There are few case reports of valproate encephalopathy reporting normal ammonia levels.⁶ In this patient, the normal

ammonia level was likely secondary to subtherapeutic valproate levels, which could be explained by the patient's increasingly poor compliance with medication with progressive confusion and aggression.

There is a common pathway through which both potential causes for this presentation may be synergistic in their effects. NMDA receptor encephalitis is mediated through NMDA receptors. Acute ammonium neurotoxicity has also been shown to be mediated through NMDA receptors in animal models.⁷ Valproate may have resulted in hyperammonaemia in this patient when her compliance was better and, coupled with a low level of NMDA receptor antibodies, may have resulted in the development of this clinical picture.

While the diagnosis of hemiplegic migraine was previously considered, the patient has not had any similar attacks of focal weakness since stopping valproate. There is the possibility of two separate pathological processes, or that possibility that this was an initial symptom of an NMDA receptor encephalitis.

The limitations of this case are a lack of serial valproate and ammonia levels and a lack of cerebrospinal fluid NMDA titre. While it would be preferable for evidence from cerebrospinal fluid to be present, and it would be a good practice to do so, a recent review did not show any benefit over serum antibodies.⁵ The patient refused subsequent blood tests and malignancy screen in the outpatient clinic, but we continue to follow-up her.

Learning points

- ▶ Subacute confusion has a wide differential diagnosis.
- ▶ Medications should be examined for clues to aetiology of confusional states.
- ▶ If there is a high index of suspicion for autoimmune encephalitis, cerebrospinal fluid as well as serum should be checked for antibodies.

Contributors SB prepared the first draft of this manuscript. MM, DS and VR edited this draft. SB and VR revised the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Neary D, Snowden JS. Sorting out subacute encephalopathy. *Pract Neurol* 2003;3:268–81.
- 2 Dealberto M-JCC. Valproate-induced hyperammonaemic encephalopathy: review of 14 cases in the psychiatric setting. *Int Clin Psychopharmacol* 2007;22:330–7.
- 3 Segura-Bruna N, Rodríguez-Campello A, Puente V, *et al*. Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand* 2006;114:1–7.
- 4 Sousa C. Valproic acid-induced hyperammonemic encephalopathy—a potentially fatal adverse drug reaction. *SpringerPlus* 2013;2:13.
- 5 Irani SR, Bera K, Waters P, *et al*. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010;133:1655–67.
- 6 Beyenburg S, Back C, Diederich N, *et al*. Is valproate encephalopathy under-recognised in older people? A case series. *Age Ageing* 2007;36:344–6.
- 7 Hermenegildo C, Marcaida G, Montoliu C, *et al*. NMDA receptor antagonists prevent acute ammonia toxicity in mice. *Neurochem Res* 1996;21:1237–44.

Copyright 2014 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