Clinical & Experimental
Neuroimmunology

Clinical and Experimental Neuroimmunology **6** (2015) 83–88

CASE REPORT

New diagnostic criteria could distinguish common variable immunodeficiency disorder from anticonvulsant-induced hypogammaglobulinemia

Rohan Ameratunga,[1,2] Karen Lindsay,[1] See-Tarn Woon,[2] Anthony Jordan,[1] Neil E. Anderson[3] and Wikke Koopmans[2]

[1]Department of Clinical Immunology, Auckland Hospital, Grafton, Auckland, New Zealand, [2]Department of Virology and Immunology, Auckland Hospital, Grafton, Auckland, New Zealand, [3]Department of Neurology, Auckland Hospital, Grafton, Auckland, New Zealand

Keywords
anticonvulsants; common variable immunodeficiency disorder; hypogammaglobulinemia

Correspondence
Rohan Ameratunga, PhD, Department of Clinical Immunology, Auckland Hospital, Park Road, Grafton 1010, Auckland, New Zealand.
Tel: +64-9-307-4949 ext. 22106
Fax: +64-9-307-2826
Email: rohana@adhb.govt.nz

Received: 30 March 2014; revised: 1 May 2014; accepted: 7 May 2014.

Abstract

Hypogammaglobulinemia is a well-recognized complication of long-term anticonvulsant drug use. Stopping or changing the anticonvulsant might result in resolution of the hypogammaglobulinemia. We determined the utility of our new diagnostic criteria for common variable immunodeficiency disorder (CVID) in a patient suffering from profound hypogammaglobulinemia who was taking anticonvulsants. Application of these criteria confirmed our patient had underlying CVID, making complete recovery of her immunoglobulins unlikely. Changing her drugs did not completely resolve her immune deficiency, and her seizure control deteriorated during this time. The partial recovery of her immunoglobulins showed that the anticonvulsants were also contributing to her hypogammaglobulinemia. In conclusion, the new diagnostic criteria we have proposed could identify patients with CVID taking anticonvulsants with greater precision, and will provide useful prognostic information. This might improve patient safety.

Introduction

Apart from primary immune deficiency diseases, there are a variety of secondary causes of hypogammaglobulinemia including drug- and virus-induced disorders, as well as gut and renal loss. In older patients, malignancy needs to be excluded.

Drugs are well-recognized causes of secondary hypogammaglobulinemia.[1,2] Anticonvulsants in particular have been associated with secondary hypogammaglobulinemia.[3,4] Most of the commonly prescribed anticonvulsants have been associated with hypogammaglobulinemia. Phenytoin appears to cause immunoglobulin A (IgA) deficiency, whereas carbamazepine tends to cause hypogammaglobulinemia from B cell depletion.[5,6] Reductions in immunoglobulins have also been described in anticonvulsant hypersensitivity syndrome.[7] Discontinuation of the drug can result in complete normalization of immunoglobulin levels.[3,4] However, changing or stopping anticonvulsants might increase the risk of morbidity and mortality from seizures.

It is imperative to exclude other causes of hypogammaglobulinemia. If another cause is identified, stopping or changing the anticonvulsant might be less critical. In most cases, the main differential diagnosis for anticonvulsant-induced hypogammaglobulinemia is common variable immunodeficiency disorder (CVID). CVID is the commonest symptomatic primary immune defect in adults. It probably represents a heterogeneous group of disorders culminating in late-onset antibody failure (LOAF). The standard of care for these patients is life-long intravenous (IVIG) or subcutaneous (scIg) immunoglobulin replacement to reduce the frequency and severity of infections. The cause of CVID is unknown, and there is no single test that will confirm the diagnosis.

The European Society for Immune Deficiency (ESID) and the Pan American Group for Immune Deficiency (PAGID) published diagnostic criteria for CVID in 1999.[8] The ESID/PAGID criteria comprise

three components: (i) hypogammaglobulinemia with immunoglobulin G (IgG) levels two standard deviations below the mean (IgG <7–8 g/L); (ii) impaired vaccine responses or absent isohemagglutinins; and (iii) exclusion of other causes of hypogammaglobulinemia.[9] Clinical sequelae and the characteristic histological features CVID were not included in the criteria.

We have recently proposed new diagnostic criteria for CVID based on both clinical and laboratory features of the disorder (Table 1).[10,11] The main difference is our emphasis on clinical immune system failure (ISF) with an increased susceptibility to infections or autoimmunity. Other characteristic features of CVID, including the relatively specific histological lesions, are also included in the diagnostic criteria. Because of the difficulties in interpreting vaccine responses, there is less emphasis on this aspect of the diagnosis in these patients.[10] The application of these criteria might have particular value in patients with secondary hypogammaglobulinemia, and are applicable to patients with anticonvulsant-induced hypogammaglobulinemia.[1] Careful review of category C and D criteria could help identify secondary causes of hypogammaglobulinemia.[1]

As will be shown here, these criteria could be useful in identifying CVID in patients who are already taking anticonvulsant drugs, where the hypogammaglobulinemia is irreversible even after stopping or changing the drug. This could allow more informed decisions to be made about stopping or changing anticonvulsants. We believe this might result in improved quality of care and patient safety.

Table 1 Proposed diagnostic criteria for common variable immunodeficiency disorder

A. Must meet all major criteria
Hypogammaglobulinemia IgG <5 g/L
No other cause identified for immune defect
Age >4 years
B. Sequelae directly attributable to immune system failure (1 or more)
Recurrent, severe or unusual infections
Poor response to antibiotics
Breakthrough infections in spite of prophylactic antibiotics
Infections in spite of appropriate vaccination e.g. HPV disease
Bronchiectasis and/or chronic sinus disease
Inflammatory disorders or autoimmunity
C. Supportive laboratory evidence (3 or more criteria)
Concomitant reduction or deficiency of IgA (<0.8 g/L) and/or IgM (<0.4 g/L)
Presence of B cells, but reduced memory B cell subsets and/or increased CD21 low subsets by flow cytometry
IgG3 deficiency (<0.2 g/L)
Impaired vaccine responses compared to age-matched controls
Transient vaccine responses compared with age-matched controls
Absent isohemagglutinins (if not blood group AB)
Serological evidence of significant autoimmunity e.g. Coombes test
Sequence variations of genes predisposing to CVID e.g. *TACI*, *BAFFR*, *MSH5* etc
D. Presence of relatively specific histological markers of CVID (not required for diagnosis but presence increases diagnostic certainty)
Lymphoid interstitial pneumonitis
Granulomatous disorder
Nodular regenerative hyperplasia of the liver
Nodular lymphoid hyperplasia of the gut
Absence of plasma cells on gut biopsy

HPV, human papillomavirus; IgA, immunoglobulin A; IgM, immunoglobulin M.

Meeting criteria in categories ABC or ABD indicates probable common variable immunodeficiency disorder (CVID). Patients meeting criteria ABC and ABD should be treated with intravenous or subcutaneous immunoglobulin. Patients meeting criteria A alone, AB or AC or AD, but not B, are termed possible CVID. Some of these patients might need to be treated with intravenous or subcutaneous immunoglobulin. Patients with levels of immunoglobulin G (IgG) >5 g/L not meeting any other criteria are termed hypogammaglobulinemia of uncertain significance (HGUS).[18–37]

Case report

A 37-year-old woman initially presented to the neurology department at the age of 14 years with temporal lobe epilepsy. She had suffered six febrile convulsions before the age of 5 years, and then developed complex partial seizures when she was aged 14 years. Some partial seizures had progressed to generalized tonic–clonic convulsions. Magnetic resonance imaging showed increased signal and mild atrophy of the left hippocampus, and an electroencephalogram confirmed there were frequent epileptiform discharges in the left temporal region.

The patient was initially treated with sodium valproate, but she was not able to tolerate this on account of depression. Subsequently, she was given phenytoin and then changed to carbamazepine, but this was discontinued when she developed liver dysfunction. She was then treated with lamotrigine and clobazam. She continued to have poor seizure control, and underwent a left anterior temporal lobectomy and amygdalo-hippocampectomy. After one seizure in the immediate postoperative period, she became seizure-free. She continued to take lamotrigine.

At the age of 33 years, the patient became progressively dyspneic. Bibasal interstitial lung disease was identified on high resolution computed tomography of the thorax. A thorascopic wedge biopsy confirmed the presence of lymphoid interstitial pneumonitis (LIP). She was noted to be agammaglobulinemic with absent IgG (<1.5 g/L, normal range 8–16 g/L), IgA (<0.07 g/L, normal range >0.8 g/L) and immu-

noglobulin M (<0.2 g/L, normal range >0.4 g/L). She had a benign infectious history. She had rarely required antibiotics, and was not suffering from suppurative respiratory tract disease. She was blood group O negative, and her memory B cells and switched memory B cells were reduced. The important immunological findings are shown in Table 2.

Because of our previous experience of a patient with reversible hypogammaglobulinemia induced by lamotrigine, the present patient was gradually weaned off lamotrigine, and gabapentin was commenced.[3] The change in treatment was associated with a recurrence of frequent complex partial seizures and several secondarily generalized tonic–clonic convulsions. She was placed on levetiracetam, and since then she has remained free of seizures She did not have any adverse effects from levetiracetam.

Several weeks after discovery of her agammaglobulinemia, she started to experience recurrent upper respiratory tract infections. After stopping lamotrigine, the serum IgG increased to 3 g/L over several months, but she remained IgA deficient. Serum immunoglobulin M levels returned to the normal range (0.67 g/L). She had excellent vaccine responses to *Haemophilus influenzae* type B (HIB) and tetanus, but poor responses to diphtheria and Pneumovax (Table 2). Almost 1 year after stopping her lamotrigine, she commenced treatment with IVIG and she has remained well. There was a marked reduction in the frequency of upper respiratory tract infections with regular IVIG.

More recently, the patient suffered from acute appendicitis. Histological review of the appendix showed the presence of plasma cells, which can sometimes be seen in patients with CVID.[12]

Table 2 Important laboratory results

Immunoglobulins	Patient	Reference interval
IgG	<0.15 g/L	>8 g/L
IgA	<0.07 g/L	>0.8 g/L
IgM	<0.1 g/L	>0.4 g/L
Vaccine responses	**Pre-vaccine**	**Post-vaccine**
H. influenzae type B antibodies	<0.11 μg/mL	6.94 μg/mL
Diphtheria antibodies	<0.004 IU/mL	0.03 IU/mL
Tetanus antibodies	0.07 IU/mL	>7 IU/mL
Pneumococcal responses (Pneumovax)	0/23	0/23
Cell markers	**Patient**	**Reference interval**
CD4	1861 × 0^6/L	500–1650 × 10^6/L
CD8	700 × 10^6/L	210–1200 × 10^6/L
CD3	2769 × 10^6/L	780–2600 × 10^6/L
CD19	110 × 10^6/L	80–600 × 10^6/L
CD56	304 × 10^6/L	40–600 × 10^6/L
Switched memory B cells (CD19+CD27+IgD−)	1.8%	5–21%

When first seen, the patient was agammaglobulinemic. Vaccine responses were undertaken after she stopped lamotrigine. She was immunized with diphtheria–tetanus toxoids, *Haemophilus influenzae* type B and Pneumovax. The response to the Pneumovax is shown by the number of serotypes reaching 1.3 μg/mL. Expected levels for tetanus and diphtheria antibodies are 1 IU/mL and 1 μg/mL for *Haemophilus influenzae* type B.

Discussion

A trial of discontinuing anticonvulsant therapy can lead to significant morbidity in the form of seizures and disruption to the patient's quality of life. Clinical features that assist in making the diagnosis of CVID and starting IVIG would help guide clinicians managing patients in this challenging scenario. Ameratunga et al.[11] criteria for the diagnosis of CVID include most of the characteristic laboratory and clinical features of the condition (Table 1). In order to meet a diagnosis of probable CVID, all patients must meet the major criteria in category A. Patients must be over 4 years-of-age to exclude most monogenic defects. The serum IgG must be below 5 g/L and secondary causes, such as anticonvulsant-induced hypogammaglobulinemia, should be excluded.[13]

Symptoms of immune system failure must also be present (category B). This usually means an increased risk of infections or autoimmunity. To qualify as having probable CVID, patients must either have characteristic laboratory findings (category C) or histological features very closely linked to CVID (category D). Patients meeting category A criteria, but not the others, are deemed to have possible CVID (Fig. 1). Patients with trivial reductions in IgG (>5 g/L) are termed hypogammaglobulinemia of uncertain significance (HGUS).

Careful analysis of category C and D criteria can help to distinguish patients with secondary hypogammaglobulinemia from those with CVID.[1] The present patient had IgA deficiency, impaired memory B cells, and very poor responses to Pneumovax and diphtheria toxin, although her responses to tetanus toxoid and HIB were preserved. We did not measure her IgG subclasses or isohemagglutinins. She had three out of eight criteria in category C, in

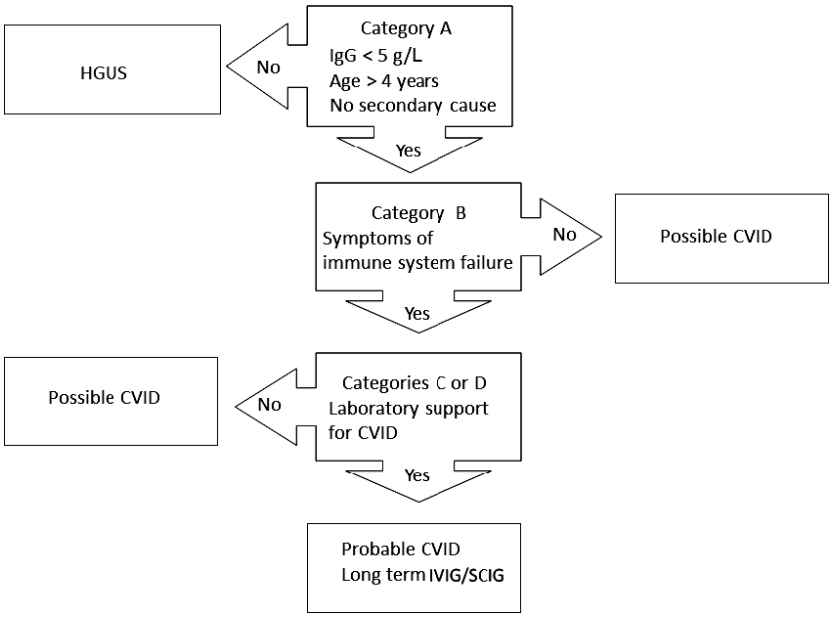

Figure 1 Diagnostic and treatment algorithm for common variable immunodeficiency disorder (CVID). Patients must meet all major criteria in category A for consideration of CVID. Category B confirms the presence of symptoms indicating immune system failure. To have probable CVID, patients must also have supportive laboratory evidence of immune system dysfunction (category C) or characteristic histological lesions of CVID (category D). Patients with mild hypogammaglobulinemia (immunoglobulin G [IgG] >5 g/L) are termed hypogammaglobulinemia of uncertain significance (HGUS). Patients meeting category A criteria, but not other criteria, are deemed to have possible CVID. Most patients with probable CVID are likely to require life-long intravenous or subcutaneous immunoglobulin. Some patients with possible CVID will require life-long intravenous or subcutaneous immunoglobulin, but most patients with HGUS are unlikely to require life-long intravenous or subcutaneous immunoglobulin replacement.

addition to meeting criteria A and B, classifying her as having probable CVID.

Importantly, the presence of symptomatic lymphoid interstitial pneumonitis (LIP) was further confirmation (category D) that she was behaving more like classical CVID and not anticonvulsant-induced hypogammaglobulinemia. This is the strongest indicator of the presence of CVID. LIP is now seen in HIV infection, as well as CVID, but has not been reported in patients prescribed anticonvulsants.[14] Our patient was HIV negative.

The present case underlines the complexity of clearly separating primary and secondary causes of hypogammaglobulinemia when patients are taking anticonvulsants. Although LIP is a classical feature confirming the presence of probable CVID, lamotrigine might also have contributed to her agammaglobulinemia, given the partial improvement in serum IgG and IgM levels on stopping the drug. There is indirect evidence from cohorts of patients with epilepsy that anticonvulsants can non-specifically suppress immunoglobulin levels.[15,16] In the presence of two disorders contributing to the hypogammaglobulinemia, the presence of LIP will identify probable CVID.

We previously published a case of severe reversible hypogammaglobulinemia in a patient prescribed lamotrigine.[3] In that patient's case, stopping the drug resulted in complete resolution of the severe hypogammaglobulinemia. He presented in the 1990s before the use of memory B cells, or vaccine responses. We cannot therefore be completely certain that these criteria would have excluded CVID in his case. He did not have any of the characteristic histological features of CVID.

We accept these criteria might not completely obviate the need to stop or change anticonvulsant therapy. They can, however, provide valuable prognostic information. The identification of probable CVID indicates complete recovery of immunoglobulins is unlikely after discontinuing the drug. These patients are likely to require long-term immunoglobulin replacement. The diagnosis of CVID might reduce the vulnerability to sepsis by shortening the interval between stopping the drug and the time immunoglobulin treatment is commenced. This might improve patient safety. Finally, the present case highlights the importance of closely monitoring patients on anticonvulsants for signs of infection, and perhaps checking immunoglobulin levels every

1–2 years even in asymptomatic patients.[17] We strongly recommend such patients are referred to a clinical immunologist with experience in dealing with both CVID and anticonvulsant-associated hypogammaglobulinemia.

Acknowledgements

We thank the patient for permission to publish this report for the benefit of others. We thank ADHB and LabPlus for on-going support.

Conflict of interest

RA has received an unrestricted educational grant from Octapharma and AJ has received a grant from CSL for educational activities.

References

1. Ameratunga R, Casey P, Parry S, Kendi C. Hypogammaglobulinemia factitia. Munchausen syndrome presenting as Common Variable Immune Deficiency. *Allergy Asthma and Clin Immunol*. 2013; **9**: 36–41.
2. Duraisingham SS, Buckland MS, Grigoriadou S, Longhurst HJ. Secondary antibody deficiency. *Expert Rev Clin Immunol*. 2014; **10**: 583–91.
3. Smith J, Fernando T, McGrath N, Ameratunga R. Lamotrigine-induced common variable immune deficiency. *Neurology*. 2004; **62**: 833–4.
4. Pereira LF, Sanchez JF. Reversible panhypogammaglobulinemia associated with phenytoin treatment. *Scand J Infect Dis*. 2002; **34**: 785–7.
5. Hoshino C, Hoshi T. Carbamazepine-induced agammaglobulinaemia clinically mimicking diffuse panbronchiolitis. *BMJ Case Rep*. 2011; **2011**: pii: bcr1120103535.
6. Yamamoto T, Uchiyama T, Takahashi H, Himuro K, Kanai K, Kuwabara S. B cell aplasia and hypogammaglobulinemia after carbamazepine treatment. *Intern Med*. 2010; **49**: 707–8.
7. Gaig P, Garcia-Ortega P, Baltasar M, Bartra J. Drug neosensitization during anticonvulsant hypersensitivity syndrome. *J Investig Allergol Clin Immunol*. 2006; **16**: 321–6.
8. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol*. 1999; **93**: 190–7.
9. Agarwal S, Cunningham-Rundles C. Assessment and clinical interpretation of reduced IgG values. *Ann Allergy Asthma Immunol*. 2007; **99**: 281–3.
10. Ameratunga R, Woon ST, Gillis D, Koopmans W, Steele R. New diagnostic criteria for common variable immune deficiency (CVID), which may assist with decisions to treat with intravenous or subcutaneous immunoglobulin. *Clin Exp Immunol*. 2013; **174**: 203–11.
11. Ameratunga R, Woon ST, Gillis D, Koopmans W, Steele R. New diagnostic criteria for CVID. *Expert Rev Clin Immunol*. 2014; **10**: 183–6.
12. Daniels JA, Lederman HM, Maitra A, Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. *Am J Surg Pathol*. 2007; **31**: 1800–12.
13. Oksenhendler E, Gerard L, Fieschi C, et al. Infections in 252 patients with common variable immunodeficiency. *Clin Infect Dis*. 2008; **46**: 1547–54.
14. Zar HJ. Chronic lung disease in human immunodeficiency virus (HIV) infected children. *Pediatr Pulmonol*. 2008; **43**: 1–10.
15. Ashrafi M, Hosseini SA, Abolmaali S, et al. Effect of antiepileptic drugs on serum immunoglobulin levels in children. *Acta Neurol Belg*. 2010; **110**: 65–70.
16. Svalheim S, Mushtaq U, Mochol M, et al. Reduced immunoglobulin levels in epilepsy patients treated with levetiracetam, lamotrigine, or carbamazepine. *Acta Neurol Scand Suppl*. 2013; **127**: 11–5.
17. Castro AP, Redmershi MG, Pastorino AC, de Paz JA, Fomin AB, Jacob CM. Secondary hypogammaglobilinemia after use of carbamazepine: case report and review. *Rev Hosp Clin Fac Med Sao Paulo*. 2001; **56**: 189–92.
18. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. *Br J Haematol*. 2009; **145**: 709–27.
19. Knight AK, Cunningham-Rundles C. Inflammatory and autoimmune complications of common variable immune deficiency. *Autoimmun Rev*. 2006; **5**: 156–9.
20. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol*. 1999; **92**: 34–48.
21. Chapel H, Lucas M, Lee M, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood*. 2008; **112**: 277–86.
22. Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. *Blood*. 2008; **111**: 77–85.
23. Abrahamian F, Agrawal S, Gupta S. Immunological and clinical profile of adult patients with selective immunoglobulin subclass deficiency: response to intravenous immunoglobulin therapy. *Clin Exp Immunol*. 2010; **159**: 344–50.
24. Olinder-Nielsen AM, Granert C, Forsberg P, Friman V, Vietorisz A, Bjorkander J. Immunoglobulin prophylaxis in 350 adults with IgG subclass deficiency and recurrent respiratory tract infections: a long-term follow-up. *Scand J Infect Dis*. 2007; **39**: 44–50.
25. Musher DM, Manof SB, Liss C, et al. Safety and antibody response, including antibody persistence for 5 years,

after primary vaccination or revaccination with pneumococcal polysaccharide vaccine in middle-aged and older adults. *J Infect Dis*. 2010; **201**: 516–24.
26. Koopmans W, Woon ST, Brooks AE, Dunbar PR, Browett P, Ameratunga R. Clinical variability of family members with the C104R mutation in transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI). *J Clin Immunol*. 2013; **33**: 68–73.
27. Tiller TL Jr, Buckley RH. Transient hypogammaglobulinemia of infancy: review of the literature, clinical and immunologic features of 11 new cases, and long-term follow-up. *J Pediatr*. 1978; **92**: 347–53.
28. Pan-Hammarstrom Q, Salzer U, Du L, et al. Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. *Nat Genet*. 2007; **39**: 429–30.
29. Salzer U, Bacchelli C, Buckridge S, et al. Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. *Blood*. 2009; **113**: 1967–76.
30. Popa V. Lymphocytic interstitial pneumonia of common variable immunodeficiency. *Ann Allergy*. 1988; **60**: 203–6.
31. Ameratunga R, Becroft DM, Hunter W. The simultaneous presentation of sarcoidosis and common variable immune deficiency. *Pathology*. 2000; **32**: 280–2.
32. Fasano MB, Sullivan KE, Sarpong SB, et al. Sarcoidosis and common variable immunodeficiency. Report of 8 cases and review of the literature. *Medicine (Baltimore)*. 1996; **75**: 251–61.
33. Fuss IJ, Friend J, Yang Z, et al. Nodular regenerative hyperplasia in common variable immunodeficiency. *J Clin Immunol*. 2013; **33**: 748–58.
34. Malamut G, Ziol M, Suarez F, et al. Nodular regenerative hyperplasia: the main liver disease in patients with primary hypogammaglobulinemia and hepatic abnormalities. *J Hepatol*. 2008; **48**: 74–82.
35. Luzi G, Zullo A, Iebba F, et al. Duodenal pathology and clinical-immunological implications in common variable immunodeficiency patients. *Am J Gastroenterol*. 2003; **98**: 118–21.
36. Malamut G, Verkarre V, Suarez F, et al. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. *Am J Gastroenterol*. 2010; **105**: 2262–75.
37. Agarwal S, Smereka P, Harpaz N, Cunningham-Rundles C, Mayer L. Characterization of immunologic defects in patients with common variable immunodeficiency (CVID) with intestinal disease. *Inflamm Bowel Dis*. 2011; **17**: 251–9.