CASE REPORT

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

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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. Phenyltoin 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. 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.

**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. Bilateral 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 immunoglobulin M (IgM) (0.07 g/L, normal range 0.4–16 g/L). The patient was treated with intravenous or subcutaneous immunoglobulin. Patients meeting criteria A alone, AB or AC, but not B, are termed possible CVID. Some of these patients might need to be treated with intravenous or subcutaneous immunoglobulin.

### Table 1 Proposed diagnostic criteria for common variable immunodeficiency disorder

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>A.</td>
<td>Must meet all major criteria</td>
</tr>
<tr>
<td>B.</td>
<td>Sequelea directly attributable to immune system failure (1 or more)</td>
</tr>
<tr>
<td>C.</td>
<td>Supportive laboratory evidence (3 or more criteria)</td>
</tr>
<tr>
<td>D.</td>
<td>Presence of relatively specific histological markers of CVID (not required for diagnosis but presence increases diagnostic certainty)</td>
</tr>
</tbody>
</table>

- Hypogammaglobulinemia: IgG <5 g/L
- No other cause identified for immune defect
- Age ≥4 years
- 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
- 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. Coombs test
- Sequence variations of genes predisposing to CVID e.g. \( TACI, BAFFR, MSH5 \), etc
- Presence of lymphoid interstitial pneumonitis
- Granulomatous disorder
- Nodular regenerative hyperplasia of the liver
- Nodular lymphoid hyperplasia of the gut
- Absence of plasma cells on gut biopsy
IgG < IgA < 9

CD56 304
CD19 110
CD3 2769
CD8 700

IgM < H. influenzae type B antibodies

CD4 1861

Tetanus antibodies 0.07 IU/mL

Pneumococcal responses < Diphtheria antibodies

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

**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

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**Table 2** Important laboratory results

<table>
<thead>
<tr>
<th>Immunoglobulins</th>
<th>Patient</th>
<th>Reference interval</th>
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<tbody>
<tr>
<td>IgG</td>
<td>&lt;0.15 g/L</td>
<td>&gt;8 g/L</td>
</tr>
<tr>
<td>IgA</td>
<td>&lt;0.07 g/L</td>
<td>&gt;0.8 g/L</td>
</tr>
<tr>
<td>IgM</td>
<td>&lt;0.1 g/L</td>
<td>&gt;0.4 g/L</td>
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<table>
<thead>
<tr>
<th>Vaccine responses</th>
<th>Pre-vaccine</th>
<th>Post-vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. influenzae type B antibodies</td>
<td>&lt;0.11 μg/mL</td>
<td>6.94 μg/mL</td>
</tr>
<tr>
<td>Diphtheria antibodies</td>
<td>&lt;0.004 IU/mL</td>
<td>0.03 IU/mL</td>
</tr>
<tr>
<td>Tetanus antibodies</td>
<td>0.07 IU/mL</td>
<td>&gt;7 IU/mL</td>
</tr>
<tr>
<td>Pneumococcal responses (Pneumovax)</td>
<td>0/23</td>
<td>0/23</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cell markers</th>
<th>Patient</th>
</tr>
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<tbody>
<tr>
<td>CD4</td>
<td>1861 × 10^6/L</td>
</tr>
<tr>
<td>CD8</td>
<td>700 × 10^6/L</td>
</tr>
<tr>
<td>CD3</td>
<td>2769 × 10^6/L</td>
</tr>
<tr>
<td>CD19</td>
<td>110 × 10^6/L</td>
</tr>
<tr>
<td>CD56</td>
<td>304 × 10^6/L</td>
</tr>
<tr>
<td>Switched memory B cells (CD19+CD27+IgD−)</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

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.
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.\textsuperscript{17} We strongly recommend such patients are referred to a clinical immunologist with experience in dealing with both CVID and anticonvulsant-associated hypogammaglobulinemia.

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

References
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.


