

# Autoimmune Encephalitis as the Sole Presentation of Common Variable Immunodeficiency: First Report in a Child

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## Abstract

**Background:** Common Variable Immunodeficiency (CVID) is a clinically heterogeneous antibody deficiency syndrome. The usual presentation is with recurrent respiratory infections. There is a strong association between CVID and autoimmune disorders. However, for CVID to present initially and solely with Autoimmune Encephalitis (AIE) is extremely rare.

**Case report:** A previously healthy three years old boy presented with acute encephalopathy and intractable seizures. His clinical features and radiological findings were highly suggestive of AIE. His evaluation has revealed findings consistent with diagnostic criteria of CVID. Recurrent infections have later on evolved during his prolonged illness.

**Discussion:** Both CVID and AIE pose a diagnostic difficulty. The prevalence of autoimmune disorders in CVID patients' cohort can be up to 50%. However, central nervous system involvement in those patients is rare. The authors are not aware of this presentation being reported in children.

**Conclusion:** In young children presenting with unexplained autoimmune encephalitis, investigations of immune system may reveal CVID, and timely and appropriate management would could be initiated.

**Keywords:** Autoimmune encephalitis; Common variable immune deficiency; Child; Intravenous immunoglobulins

## Introduction

Common variable immunodeficiency (CVID) is one of the primary immune deficiency diseases, characterized by immune deficiency, recurrent infections, autoimmunity, and high risk of cancer [1]. Its onset runs two peaks of diagnosis, first during childhood and the second between 30 and 40 years of age [2]. Recent reports indicate that autoimmune diseases are observed in 25-30% of cases<sup>3</sup>, ranking as second clinical presentation after infections [2]. They present before diagnosis of CVID in 18% and are the only presenting feature of CVID in 2.3% [3,4]. Large series of CVID reported rates of organ specific-autoimmune diseases, but did not include any data on autoimmune brain affection [3,5].

Autoimmune encephalitis (AIE) is defined as a heterogeneous group of neurological disorders characterized by cognitive and behavioral decline resulting from an immune reaction against neuronal antigens [6]. It comprises 21% of all cases of encephalitis [7]. It is. In a study by Granerod and his group, children represent around 40% of the universal cohort of patients with autoimmune encephalitis [7]. It is thought that in one third of children presenting with acute and subacute encephalitis, it could be due to autoimmune pathological processes. In this series, 50% of that cohort demonstrated positive neuronal autoimmune antibodies [7]. There are few case reports on AIE with CVID [8-10]. Furthermore, autoimmune encephalitis as the only presenting clinical feature of CVID is rarely described particularly in children. Akman, et al., described as 16 year old girl who presented with limbic encephalitis with anti-GAD antibody and CVID [11]. To the best of our knowledge, this is the first report describing the youngest patient ever presented with autoimmune disease as the sole clinical feature in CVID.

## Case Report

A 3 years old boy, previously healthy, presented with fever and increasing sleepiness for one week. It was not associated with any vomiting, visual disturbances, behavioral changes, or headaches. He

was up-to-date on his immunizations. He was born to healthy, non-consanguineous parents, and has two normal siblings. Apart from neck stiffness and lethargy, his general physical and complete neurological examinations were otherwise unremarkable. A day later he developed intractable seizures in form of right sided tonic-clonic movements, with eye deviation and lip smacking. He was transferred to the Pediatric intensive Care Unit (PICU). Since seizures were frequent and did not respond to phenytoin, phenobarbitone, and midazolam, he was intubated, sedated and started on mechanical ventilation. This refractory status epilepticus which lasted for several weeks in spite of treatment with multiple anti-epileptic medications including Levetiracetam, Lacosamide, Topiramate, Clobazam, Ketogenic diet, and several anesthetic agents. He also received steroids, intravenous immunoglobulins (IVIG) and plasmapheresis. A tracheostomy and PEG tube were inserted. EEG showed Continuous spike and slow wave and MRI showed bilateral basal ganglia high signal followed by brain atrophy.

Initial laboratory investigations revealed CBC with differential, serum electrolytes, liver function tests, ESR, C-reactive protein, and coagulation profile all within normal limits. Qualitative PCR studies on nasopharyngeal secretions were negative for influenza viruses, parainfluenza viruses, Corona viruses, enterovirus, human metpneumovirus, Boca virus, mycoplasma, adenovirus and pandemic H1N1 viruses. CSF studies for Gram stain, cells, protein, glucose,

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cultures, amino acids, and PCR for cytomegalovirus, Epstein-Bar virus, adenovirus, herpes simplex virus 1 and 2, varicella-zoster virus, enterovirus, mumps, and parecho virus all were negative. CSF for fungal and tuberculous infections was negative as well later on. Initial blood, urine and CSF cultures all were not growing any organisms. CSF for paraneoplastic autoantibodies (paraneoplastic autoantibody panel for ANNA-1, ANNA-2, ANNA-3, AGNA-1, PCA-1, PCA-2, PCA-Tr, Amphiphysin, and CRMP-5-IgG) were all negative. Serums amino acids, ammonia, and lactic acid were normal. Serum IgG was low (208 mg/dl), IgA undetectable (less than 6.2 mg/d), IgM low (22.4 mg/dl). Serum IgG subclasses were low: IgG1 was 133 mg/dl and IgG3 8.5 mg/dl. Lymphocyte subsets revealed elevated CD3 79.4%, but low CD19 13%. However, CD4, CD8, CD4/CD8 ratio, and CD56 were normal. Anti-vaccine antibodies revealed normal titers against diphtheria, tetanus, *H. influenzae* and *pneumococci*. Other serological workup revealed negative titers of anti-smooth antibodies, anti-LKM, anti-endomesial, anti-tissue transglutaminase IgG and IgA, anti-cardiolipin IgM & IgG, rheumatoid factor, anti-nuclear antibodies, anti-myeloperoxidase, anti-proteinase 3, and ANCA. C3 and C4 were normal.

During his long eight weeks hospitalization stay, he developed few and separate episodes of infections with positive blood cultures for *S. marcescens*, *M. luteus*, and *C. parapsilosis*. There were also two separate positive *E. coli* cultures from urine, so indwelling urinary catheter was changed to intermittent cauterization. Cultures were checked through both automated and manual maneuvers. No other pathogen had been isolated. Central catheter tip was negative in culture studies. Cranial MRI showed global cerebral atrophic changes and bilateral signal intensity in basal ganglia and thalami consistent with global brain injury. The patient slowly went into stable minimal responsive state. He was moved to the pediatric rehabilitation therapy. He remained on three anti-epileptic medications. He was started on replacement intravenous immunoglobulins (IVIG) as he met the diagnostic criteria of CVID [12,13].

## Discussion

Although autoimmunity is an integral feature of CVID, the exact pathogenesis mechanisms are not well defined from molecular perspectives. However, there is recent studies revealed the possible role of abnormal homeostatic, immune dysregulatory mechanisms involving mainly B-cells [14,15], in addition to T cells, antigen receptor signaling, TLR signal or others [16]. This results in tissue- or organ-specific autoimmune antibodies.

AIE, defined as a group of disorders characterized by clinical features of central nervous system disease, such as extra-limbic, limbic, basal ganglia, autonomic structures or others, and presence of autoantibodies directed extracellular, cell membrane, or intracellular antigens of these structures [16]. These autoantibodies result from dysregulated T-cell or antibody-mediated immune mechanisms [17]. Rate of recovery of these autoantibodies from the serum or the CSF is variable [17]. These autoantibodies seem to be a marker of autoimmune disease activity rather than directly causing neuronal damage [18]. Sometimes, the diagnosis of AIE, particularly in children, is made in absence of these autoantibodies [19] after exclusion of other causes of acute encephalopathy such as infective, toxic, metabolic and epileptic.

Happe and Husstedt have reported a 31-year old female who presented with acute encephalomyelitis [8]. She had an elevated CSF protein and IgM fraction. Being diagnosed with CVID since age of 19 years, the cause of her encephalitis was presumed to be autoimmune. Vella et al., reported as 20 year girl who developed acute disseminated

encephalomyelitis as the first clinical manifestation of CVID9. Akman et al., reported a 16 year old female who was diagnosed with acute limbic encephalitis as confirmed by an elevated anti-GAD antibodies in serum and CSF. She had family history of IgA deficiency, pernicious anemia and leukemia. Her immunological investigations were compatible with diagnosis of CVID11.

Our patient is 3 year old at time of presentation, and it is known that first peak of CVID is during the first 5 years [2]. Our patient had low serum IgG, IgA, IgM and IgG subclasses and IgG subclasses, and abnormal lymphocyte subsets. His clinical presentation in the absence of any other etiology makes autoimmune encephalitis the most likely diagnosis even in absence of autoantibodies in serum and CSF.

In young children, like our case, there are few challenges in establishing diagnoses of both AIE and CVID. For example, children presenting with hypogammaglobulinemia and normal vaccine antibody responses like our patient, progress to CVID [20]. Besides, there are many difficulties interpreting the vaccine responses in CVID13. Patient age (>4 years) is included in diagnostic criteria of CVID13. However, revised ESID diagnostic criteria of CVID diagnosis state that diagnosis should be established after the 4th year of life although symptoms may be present before [21]. Another related issue is the fact that CVID is heterogeneous group of diseases of diverse genetic mutations and variable clinical presentations that complicate the diagnosis prompted researchers to phenotypically categorize CVID depending on presenting features of infections, inflammation/autoimmunity or others [3]. Besides, as CVID is not a single gene defect, the molecular approaches for defining the genetic defects are impractical are only useful in a minority of cases [22].

## Conclusion

This case report emphasizes that even in young children AIE could be the only presenting feature of CVID. In patients presenting with unexplained encephalitis evaluation of the immune system may disclose CVID so that early management would improve disease course and prevent further complications.

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