

## CASE REPORT

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# A Case of Hypogammaglobulinemia with Enteroviral Meningoencephalitis, Associated with Increased Adenosine Deaminase in Cerebrospinal Fluid

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## ABSTRACT

We describe the development of enterovirus meningoencephalitis associated with increased adenosine deaminase in cerebrospinal fluid of a 12-year-old boy, a known case of hypogammaglobulinemia despite monthly replacement of IVIg.

The patient was referred to our center with fever, headache and vomiting for 10 days. CSF analysis was compatible with aseptic meningoencephalitis but high CSF protein (>200mg/dl) and high level of adenosine deaminase in CSF (30IU/L) were against the diagnosis of simple viral meningoencephalitis. Nested PCR of CSF for enterovirus was positive. Treatment with daily high-dose IVIg was commenced, with significant clinical improvement.

For patients with increased ADA and lymphocytic pleocytosis in CSF, differential diagnoses should include enteroviral meningitis. Antibodies, although crucial, cannot on their own prevent enteroviral infection in some hypogammaglobulinemic patients.

**Key words:** Adenosine deaminase; Cerebrospinal fluid; Hypogammaglobulinemia; Enteroviral meningoencephalitis

## INTRODUCTION

Chronic enteroviral meningoencephalitis is one of the complications of agammaglobulinemia.<sup>1</sup> Meningoencephalitis due to enteroviruses is particularly serious when occurring in patients with agammaglobulinaemia.<sup>2</sup>

Intravenous immunoglobulin (IVIg) has been used for many years in the treatment of primary antibody deficiency. However this intravenous replacement therapy does not protect against viral meningoencephalitis.<sup>3</sup> Most published reports have referred to its occurrence in patients on no replacement therapy or only on intramuscular immunoglobulin replacement.<sup>4</sup>

Adenosine deaminase is an enzyme which catalyzes the conversion of adenosine and 2' deoxyadenosine to inosine and 2' deoxyinosine, respectively. The major

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sources of serum ADA may be lymphocytes or the cells of monocyte -macrophage series. Cerebrospinal fluid (CSF) adenosine deaminase (ADA) activities are known to be raised in tuberculous meningitis and their levels have been suggested to help differentiate tuberculous meningitis from other forms of meningitis.<sup>5</sup> We report the development of enteroviral meningoencephalitis in a 12 year old boy, a case of hypogamaglobulinemia with increased adenodeaminase in cerebrospinal fluid that was on regular IVIg treatment for the past 5 years.

### CASE REPORT

A 12 year old boy, known case of hypogamaglobulinemia diagnosed when he was 5 years old, presented with recurrent sinopulmonary infection. Investigation revealed panhypogammaglobulinemia with no circulating B cells (CD19% was zero). Other CD markers were: CD3 %80.5, CD4 %35.5 and CD8 %52.5. IgG was 650mg/dl. IgA and IgM were lower than 10 mg/dl. Since then he was on regular Ig IV (OCTAPHARMA AG, Switzerland) replacement of 10 gram monthly. Within this period he had several hospital admissions due to meningitis, sinusitis and subdural abscess, the latter occurred 2 years back and needed surgical intervention. Thereafter he was well till October 2007, when he was referred to our center with a history of a headache of 10 days, vomiting and fever. His parents are unrelated and there was no family history of immunodeficiency. On physical examination of head and neck there was no lymphadenopathy and tonsil were not detectable either. Since the patient was suspicious to have bacterial meningitis, blood and CSF cultures were requested and intravenous vancomycin and ceftriaxon were started. Hemoglobin was 11.3g/dl, leukocytes 4300/mm<sup>3</sup> (56% neutrophils, 36% lymphocytes, 2% stabs, 2% monocytes, 2% eosinophils), platelets 247000/mm<sup>3</sup>, ESR 10mm/hour, C-reactive protein 12mg/L, febrile agglotination test and CSF serology for brucellosis were negative and tuberculin skin test was also negative. Brain MRI revealed communicating hydrocephalus. Cerebrospinal fluid analysis revealed total cell count 410/mm<sup>3</sup>, leukocytes 410/mm<sup>3</sup> with 70% lymphocytes, sugar 65mg/dl, protein 200mg/dl. Level of adenosine deaminase (ADA) in cerebrospinal fluid was 30IU/L. Gram stain, Indian ink stain; acid fast stain and bacterial culture of Cerebrospinal fluid were

negative. cerebrospinal fluid cytology was normal. Nested PCR of cerebrospinal fluid for enterovirus was positive. Antibiotics were discontinued and treatment with daily high-dose Ig IV (600mg/kg/day) for 6 days was commenced, which led to significant clinical improvement.

### DISCUSSION

Our patient developed enteroviral meningoencephalitis despite regular 400 mg/kg Ig IV replacement monthly. This may suggest that this amount of antibody, although crucial, cannot by itself prevent enteroviral infection in some patients. The significant clinical improvement seen in our patient within 6 days with the use of high-dose IVIg alone was probably due to the antiinflammatory effect of Ig IV. Ig IV contains antibodies directed against IL-1, IL-2 and TNF that could alter cytokine concentration in patients with enteroviral brain stem encephalitis.<sup>6</sup> Moreover, significant extravasations of Ig IV to the CNS can occur when blood brain barrier function is compromised during encephalomyelitis.<sup>7</sup> Successful treatment of chronic enteroviral meningoencephalitis with high-dose Ig IV alone has been documented previously.<sup>8-10</sup> The successful use of intraventricular or intrathecal Ig in conjunction with Ig IV in eradicating virus and producing varying degrees of clinical improvement has been reported in some patients.<sup>11,12</sup>

The major sources of serum ADA may be lymphocytes or the monocyte -macrophage series of cells. Increased ADA in rare cases of bacterial meningitis could be due to a damage to oligodendroglia and endothelial cells or to intrathecal synthesis in response to bacterial antigens.<sup>13</sup> This might be the case also with enteroviral meningitis. Cerebrospinal fluid (CSF) adenosine deaminase (ADA) activities are known to be raised in tuberculous meningitis and their levels have been suggested to help differentiate tuberculous meningitis from other forms of meningitis.<sup>5</sup> Our patient's CSF characteristics of increased ADA and lymphocytic pleocytosis made it difficult to rule out tuberculous meningitis and neurobrucellosis, but tuberculin skin test was negative and the patient recovered with no treatment for tuberculosis. Serum febrile agglotination test and CSF serology for brucellosis were also negative. Beside the causes mentioned, the increase of ADA level in CSF can also be caused by sarcoid meningitis, meningeal involvement with leukemia or lymphoma, cryptococcal

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meningitis, cerebral toxoplasmosis, cerebral infarction and neurosyphilis.<sup>13</sup>

To the best of our knowledge, this is the first case report of enteroviral meningoencephalitis in hypogammaglobulinemia, associated with increased adenosine deaminase in cerebrospinal fluid. For patients with increased ADA and lymphocytic pleocytosis in CSF, differential diagnosis should include enteroviral meningitis. The ADA levels in the CSF of numerous immunocompromised and immunocompetent patients need to be evaluated to elucidate the sensitivity of this disease marker. Antibodies, although crucial, can not without any other medication prevent enteroviral infection in some hypogammaglobulinemic patients.

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