Chronic enteroviral meningoencephalitis in a patient with Good's syndrome.

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Research Article

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Abstract

Enteroviruses are a diverse selection of viruses which include polioviruses, coxsackieviruses, echoviruses and others. Severe or persistent enteroviral infection is well-documented in patients with antibody deficiency, mostly in those with X-linked agammaglobulinemia (XLA) or following anti-CD20 monoclonal antibody therapy[1]. Here we report the first case of enteroviral meningoencephalitis in a patient with Good's syndrome and discuss the possible aetiopathogenic mechanisms involved.

Description

This male patient presented at the age of 27 with recurrent chest infections and weight loss. Two years later a diagnosis of cortical thymoma (type B2) was made and he underwent a successful surgical excision. Post-operatively he continued to have multiple infections, mainly pneumonias, and investigations revealed low serum immunoglobulins (Supplementary Table 1). He was referred to Clinical Immunology where a complete absence of peripheral B cells was identified, with minimal bronchiectasis on a thoracic CT scan. The combination of thymoma with immunodeficiency led to the diagnosis of Good's syndrome and he was commenced on immunoglobulin replacement, with prophylactic Co-Trimoxazole, to good effect.

Lower respiratory tract infections became less frequent, but he cultured *Haemophilus influenzae* in his sputum twice over the subsequent years. He also had an episode of unilateral epididymo-orchitis complicated by abscess formation. Aged 31 he developed bulbar and penile urethral strictures for which he required a urethroplasty.

Aged 36 he suffered a brief episode of right hemiparesis with dysaesthesia and dysarthria. Brain MRI, CT head, echocardiogram and carotid doppler did not reveal a cause for his symptoms and these were attributed to a transient ischemic attack. Over the following years he attended the emergency department three more times for neurological symptoms of vertigo, ataxia, dizziness and/or facial dysaesthesia, with continuing normal brain imaging.

Aged 41 he presented with an episode of facial and left upper limb dysaesthesia. A CT head was normal but an MRI at that stage revealed white matter high T2 intensity suggestive of transependymal oedema. Over the next 2 months he complained of deteriorating headaches with photophobia and was found to have a mild cognitive impairment (23/30 on Montreal Cognitive Assessment test). He was later admitted to hospital with a focal seizure, left facial weakness and dysarthria. An EEG revealed abnormal asymmetrical activity in his frontal lobe, but no seizure activity. His repeat MRI revealed progression of the previously noted abnormalities, with an enlargement of the ventricular system in keeping with hydrocephalus and a rarely described pattern of T2 high intensity in the claustrum (Figure 1). A subsequent CT head confirmed communicating hydrocephalus (Figure 1) and a lumbar puncture revealed a significantly raised CSF protein (Supplementary Table 1). CSF was lymphocytic and enterovirus was identified by PCR (non-polio, non-typable). This was confirmed in two more lumbar punctures. His blood,

throat and stool samples were consistently negative for enterovirus. His IgG trough on replacement immunoglobulin at that stage was good, >8g/L.

He was treated with levetiracetam and an experimental drug for enteroviral infection pocapavir (MedChemExpress LLC). His immunoglobulin dose was also increased and an external ventricular drain was inserted to relieve the hydrocephalus. An attempt to remove this led to re-accumulation of hydrocephalus so a permanent ventriculoperitoneal shunt was inserted. After a prolonged hospital stay he made a partial recovery but was unable to drive or work for several years. Currently, at the age of 46, he has managed to return to work and is able to drive but exhibits intermittent bilateral hand tremor.

Discussion

Enteroviral infections are a well-documented complication in XLA, causing chronic meningoencephalitis or a dermatomyositis-like syndrome[2]. Several cases of enteroviral meningoencephalitis have also been reported post-rituximab therapy, a B cell-depleting monoclonal antibody[3]. These infections tend to be more common in those either not receiving or receiving suboptimal antibody replacement, but can also be seen in patients on antibody replacement with good IgG levels.

Enteroviruses are thought to be highly cytolytic and can greatly compromise brain function. Enteroviral brain disease has a high morbidity and mortality in immunodeficiency, with a study reporting 43% mortality in these patients, usually within 2 years of diagnosis[4]. Severe long-term sequelae are also common in survivors[4]. This infection may present in an insidious manner, as is evident from the case above.

Interestingly, enteroviral infections are not encountered often in patients with antibody deficiencies with normal peripheral B cell counts, like some forms of common variable immunodeficiency (CVID). Indeed, one of the few reported cases of enteroviral encephalitis in CVID was in a patient with absent peripheral B cells[5]. Patients with antibody deficiency and low peripheral B cells are also more prone to other types of opportunistic viral infections (e.g. chronic norovirus infection)[1], which suggests an important role for B cells in antiviral immunity. These patients are also more likely to have absent serum IgA and IgM, with very poor IgG antibody responses to infection, which may explain this association, although B cells also play an important role in antiviral immunity in their role as antigen-presenting cells.

An extensive search in Medline and Embase databases (with the terms “good* syndrome”, “thymoma with immunodeficiency”, “enterovi* meningitis or encephalitis”) did not identify any previous case reports of enteroviral meningoencephalitis in Good’s syndrome[1]. Patients with Good’s syndrome characteristically exhibit hypogammaglobulinemia and very low peripheral B cells. Opportunistic infections are common in these patients (e.g. chronic or recurrent viral infections are seen in up to 40% of cases). Circulating T cell counts can also be low but the clinical implications of this seem less marked and patients with low CD4+ T cells do not appear to exhibit a higher risk for opportunistic infections in Good’s syndrome.

Overall, chronic enteroviral meningoencephalitis is an important diagnosis to consider in patients with antibody deficiency presenting with neurological symptoms, particularly in those with very low or absent peripheral B cells. The widespread use of immunoglobulin replacement has made this complication less prevalent, but it is still an important diagnosis to consider. The higher incidence of enteroviral brain infections in patients with antibody deficiency with low peripheral B cells (compared to those with normal) suggests an important role for B cell immunity in antiviral defences.

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Consent to participate:

Informed consent was obtained from all individual participants included in the study

Consent to publish:

The authors affirm that human participants provided informed consent for publication of the images in Figure 1

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Figures

Figure 1

Radiological investigations at the point of diagnosis of enteroviral meningoencephalitis: (a & b) CT head showing hydrocephalus; (c & d) MRI head showing a rarely described pattern of T2 high intensity in the claustrum (arrows) and hypointensity in the lateral ventricles.

Supplementary Files

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