Intravenous Immunoglobulin in Pediatric Neuropsychiatric Lupus Triggered by Epstein-Barr Virus Cerebral Infection

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KEY WORDS: intravenous immunoglobulin therapy (IVIG), neuropsychiatric systemic lupus erythematosus (NPSLE), Epstein-Barr virus (EBV), pediatric psychosis

IMAJ 2016; 18: 763–766

In the last few years the link between environmental factors and autoimmunity has gained increasing attention, with evidence that the immune response to infectious organisms could contribute to the onset of several autoimmune diseases. Different studies support the evidence of virus infection and particularly of Epstein-Barr virus (EBV) as a trigger of systemic lupus erythematosus (SLE) [1]. SLE is a common autoimmune disease frequently observed in childhood after the age of 5 years, with approximately 20% of cases starting before the age of 18 years, involving different organs with several clinical signs. In children, neuropsychiatric systemic lupus erythematosus (NPSLE) was found to have a frequency of 14%–95% as well as high mortality and poor treatment response [1].

We present the clinical case of a child who developed a severe clinical picture of NSLE triggered by a reactivated EBV cerebral infection, successfully treated with intravenous immunoglobulin (IVIG). To the best of our knowledge this is the first reported case of IVIG treatment for pediatric neuropsychiatric lupus infection triggered by EBV.

*The first two authors contributed equally to this study

PATIENT DESCRIPTION

A previously healthy 7 year old boy was admitted to our Pediatric Neurology Unit due to abrupt and persistent dystonic movements in the left leg associated with paresthesia and difficulty walking. His family history was positive for epilepsy (maternal grandfather) and immunological disease (his mother was affected by Hashimoto thyroiditis and autoimmune gastric atrophy). He was born at term after an uncomplicated pregnancy. His perinatal course and neurodevelopmental milestones were reported as normal. The child had an uneventful medical history except for sporadic headaches and oral ulcers. Seven days before emergence of the motor disorder he experienced some prodromal symptoms, including mild fever, pharyngitis, headache, cough and fatigue, which were treated with antibiotics. In the following days the child exhibited dystonic and uncoordinated distal jerking movements in the left arm, photophobia, diplopia and clumsiness. He was also noted to have some psychiatric symptoms: irritability, mood disturbance, psychomotor agitation and hallucinations.

On admission, the patient was afebrile and several laboratory and autoimmune tests yielded normal results [Table 1]. In particular, antiphospholipid antibodies, C3, C4 complement and lupus autoantibodies (ENA, ANA, anti-dsDNA) were negative. Cerebrospinal fluid (CSF) analysis showed pleocytosis (lymphocytes 100%), presence of oligoclonal cells and positive polymerase chain reaction for EBV infection, whereas the serology of EBV was suggestive of a reactivated infection: EBV VCA (viral capsid antigen) IgG 68.80 UA/ml, EBV nuclear antigen (EBNA) IgG > 200 UA/ml. The first brain magnetic resonance imaging (MRI) scan showed a small gliosis focus of increased T2-weighted Flair signal in the left frontal subcortical white matter and a diffuse cortical and subcortical leptomeningeal enhancement on the contrast-enhanced T1-weighted images; MRI of the medulla was normal. In keeping with the hypothesis of EBV-reactivated encephalitis, acyclovir therapy was started.

Despite the treatment, over the next few days the patient exhibited weakness and increased passive tone in the left side (both arm and leg) associated with asymmetric reflexes and choreoathetoid movements of the distal left arm. He also had visual hallucinations resembling the "Alice in Wonderland syndrome," namely, an acute persistent confused state associated with psychomotor agitation resistant to standard therapy (diazepam, propofol anesthesia, haloperidol). One month after appearance of the EBV-reactivated infection, in spite of intravenous corticosteroid treatment (methylprednisolone 1 mg/kg/day), he demonstrated a neurological condition characterized by epileptic seizures, left hemiparesis with extrapyramidal signs (cogwheel rigidity in the left side), facial spasm and dysarthria. The child also developed progressive cognitive impairment, psychosis with delirium and auditory hallucinations. Anti-epileptic therapy was begun (intravenous levetiracetam followed by oral levetiracetam and clobazam), and although there was a mild improvement the psychiatric symptoms failed to respond to antipsychotic therapy (risperidone). In

Table 1. Laboratory assessment before IVIG treatment

		At onset	One month later
Serum tests	ESR, C-reactive protein, serum lactate, hepatic enzymes, ammonium, ASO titer, rheumatoid factor, lactate, creatinine, WBC	All negative	All negative, except for ESR (32 mm)
	Serum ceruloplasmin, copper serum and urine levels	Unavailable	All negative
	Toxoplasma, HSV 1/2, CMV, VZV, HHV6, *B. borrellia*, *Mycoplasma* IgM/IgG, larva migrans, VDRL	All negative	All negative
	EBV serology	**VCA IgG 68.80 UA/ml, VCA IgM-, EBNA IgG > 200 UA/ml**	**VCA IgG 77.70 UA/ml, VCA IgM+, EBNA IgG > 200 UA/ml**
CSF analysis	Macroscopy	Mild opalescent CSF	Mild opalescent CSF
	Microscopy	Negative	No bacterial infection/**TB**
	Glucose	Negative	↑ 87 mg/dl (40–70),
	Protein	Negative	↑ 49 mg/dl (20–40),
	Lactate	Negative	Negative
	WBC	Pleocytosis 10.00/mm^3 (LY 100%)	↑ 56 **cell counts**/mm^3 (< 5)
	Oligoclonal cells	Unavailable	+ 4
	Cancer cells	Unavailable	Negative
	Blood-brain barrier	Negative	Negative
	PCR (HSV 1/2, CMV, Enterovirus Parvovirus, Enterovirus, HSV 1/2, CMV, VZV, HHV6, JCV virus, *B. borrelia*	All negative	Negative
	PCR EBV	**DNA+**	All negative **DNA+ (207 copies/ml)**
Immunological assessment	CD4/CD8 ratio	2.25 (1.10–1.80)	All negative except for:
	Anti-TPO Ab, anti-TG Ab	10.0 UA/ml, 5.41 UA/ml	**ANA+ at 1/80 dilution with speckled pattern, anti-dsDNA Ab 22.4 UA/ml, anti-nucleosome Ab120 UA/ml, cANCA 4.7 UA/ml**
	ASMA, AMA, anti-centromere, anti-SCL 70, anti-citrulline, anti-endomysial Ab, anti-Jo 1 Ab, anti-transglutaminase Ab, cryoglobulins, immune complexes, C3, C4, anti-pANCA, **ENA, ANA, anti-dsDNA**	**All negative**	
Antiphosholipid antibodies	Lupus anticoagulant, anti-β2 glycoprotein, anti-cardiolipin, anti-prothrombin antibodies	Negative	Negative
Onconeural antibodies	Anti-Yo, anti-Ri, anti-Hu, anti-CCU2, anti-AGNA, anti-Me antibodies	Unavailable	Negative
Antineuron antibodies	Anti-NMDAR, anti-GABA b, anti-Lgi-1, anti-CASPR 2 antibodies	Unavailable	Negative

Bold indicates EBV infection and **Lupus** positivity

Ab = antibodies, ERS = erythrocyte sedimentation rate, HSV = herpes simplex virus, CMV = cytomegalovirus, WBC = white blood cell count, ASMA = anti-smooth muscle antibodies, AMA = anti-mitochondrial antibodies, ENA = anti-extractable nuclear antigens antibodies, pANCA-C = anti-neutrophil cytoplasmic antibodies, dsDNA = double-stranded DNA, anti-TPO = anti-thyroid peroxidase antibodies, anti-T = anti-thyroglobulin antibodies, NMDA = N-methyl-D-aspartate, GABAB = c-aminobutyric acid receptor B, LGI1 = glioma inactivated protein-1, CASPR2 = contactin-associated protein-2, VCA = viral capsid antigen, TB = tuberculosis, VZV = varicella zoster virus, *B. borrellia* = *Borrelia burgdorferi*

the following days his clinical status was critical due to the appearance of frontal lobe syndrome signs, severe cognitive impairment, severe axial hypotonia, facial grimacing, and difficulty eating and performing activities of daily living.

Brain and medulla MRI showed persistent cortical and subcortical leptomeningeal enhancement, whereas SPECT and PET-CT (positron emission computed tomography) total body imaging excluded a paraneoplastic syndrome and alterations in both cerebral perfusion and metabolism. Bone marrow biopsy was negative for lymphoproliferative disorder or B lymphocyte clonality. Electromyography, sensory/motor nerve conduction and auditory evoked potentials were normal. Only the motor evoked potential study showed cortical dysfunction. He presented also with malar rash, arthralgia and oral ulcers. When immunological assessment was repeated, ANA, anti-dsDNA and antinucleosome antibodies were positive (ANA at 1/80 dilution with speckled pattern, anti-dsDNA antibodies 22.4 AU/ml, antinucleosome antibodies 120 AU/ml). Other laboratory tests, including complement C3-C4, renal function (creatinine levels), antiphospholipid antibodies and white blood cell count (WBC), were negative except for erythrocyte sedimentation rate (ESR). According to criteria of the American College of Rheumatology (ACR, 1997) and the International Collaborating Clinics Classification (SLICC, 2012), NPLES diagnosis was fulfilled due to the presence of three clinical criteria (malar rush, oral ulcers, neurological involvement) and two immunological criteria (ANA, anti-dsDNA positivity). The presence of antinucleosome antibody positivity, known to be a sensitive and highly specific marker for SLE (mainly lupus nephritis), further confirmed this diagnosis.

In view of clinical worsening and immune mediated etiopathogenesis, intravenous immunoglobulin therapy (IVIG) was

started (0.4 g/kg/day) for 5 days, repeated 20 days later for a total of three times. Steroids were discontinued following therapy with IVIG. During the course of the three IVIG administrations, the child showed a progressive improvement in both clinical and immunological tests with progressive reduction of lupus antibody titers in subsequent months. He started to speak fluently, regained walking ability, improved in activities of daily living and in behavior with a reduction of psychotic symptoms.

One year later, there was no evidence of hemiparesis and cognitive assessment was in the borderline range, with difficulties mainly in working memory and visuoperceptual ability. The child continued to have episodic malar rash without the presence of renal or respiratory symptoms or levels of active disease required for corticosteroid therapy. Laboratory tests revealed only ANA positivity at a dilution of 1/40 (non-specific speckled pattern) with the other LES autoantibodies in the normal range.

COMMENT

Autoimmune diseases are believed to result from interactions between genetic and environmental factors. Among them are ultraviolet light, drugs, vaccinations, smoking, and infectious pathogens, which could directly affect the immune system or induce epigenetic changes modulating gene expression. Infections could act as environmental triggers inducing or promoting SLE in genetically predisposed individuals. EBV is one of the environmental risk factors most closely associated with SLE [1]. Several case-control studies provide more evidence of EBV infection as a triggering pathogenic factor in adult and juvenile SLE patients, i.e., abnormally elevated EBV load in their blood and higher EBV antibody titer as compared with healthy controls [1,2]. Conversely, other cohort studies did not find evidence of a correlation between primary infection of EBV and SLE, suggesting an immune dysregulation underlying the immune status of SLE patients. However, the role of latent and EBV reactivation in the autoimmune response of SLE was recently investigated and our clinical case seems to confirm this association.

As with other types of herpes, periodic EBV reactivation can occur, stimulating the immune system and leading to autoimmune disease in genetically predisposed individuals. After primary infection and the lytic phase, autoreactive B cells proliferate, leading to latent infection. EBV-infected memory B cells are resistant to apoptosis due to the expression of virus-encoded anti-apoptotic molecules. These cells act as antigen-presenting cells stimulating T cell migration and production of cytokines such as IL-10, which promote EBV-infected B cell proliferation and inhibit cytotoxic T cell lysis of EBV-infected cells [1,2]. Specifically, it was found that patients with SLE, compared with healthy controls, had an increased frequency of EBV specific memory CD4+T cells that produce interferon as a compensatory mechanism for an inadequate CD8+ T cell response against EBV, suggesting defective control of latent EBV infection in SLE [2]. These mechanisms could lead to subsequent infection and transformation events resulting in chronic damage and altered autoimmune responses. EBV antigens can lead to autoimmunity by structural molecular mimicry with common SLE antigens. It is known that antibodies against EBNA1 could cross-react with the spliceosomes SmD and 60 Kd Ro [1,2], and in a murine study anti-EBNA antibodies produced after immunization cross-react with dsDNA leading to development of lupus antibodies.

EBV could also act through "functional" molecular mimicry, with critical immune regulatory components interfering with immune surveillance and latent process through two latent membrane proteins (LMP-1, 2) and by transactivation of HERV-K18 superantigen activity [2]. Anti-EBNA-1 antibodies are expressed in the latent phase of EBV infection and are responsible for tethering the EBV genome to chromosome-altering gene expression. In our patient, the presence of anti-EBNA antibodies was suggestive of a previous infection, and the presence of EBV DNA in the CSF confirmed EBV encephalitis that preceded the neuropsychiatric symptoms and the autoantibodies typical of SLE (anti-dsDNA, ANA, and antinucleosome antibodies).

NPSLE is a common SLE manifestation occurring mainly in children at SLE onset with different symptoms: psychosis, affective disorders, seizures, cerebrovascular disease, movement disorder, acute confused state, organic brain syndrome (disturbance of memory, perception, orientation, or other cognitive function) and neuropathies [1]. These clinical sequelae are thought to arise from vascular abnormalities or an interaction of neuronal autoantibodies with neuronal and glial cells that lead to diffuse neuropsychiatric manifestations, such as psychosis and acute confused state because of the development of inflammatory mediators. NPSLE has been reported to occur more frequently in pediatric SLE patients (22–95%) and is correlated with higher mortality and poor outcome due to its resistance to treatment [1].

Our patient had a severe neuropsychiatric condition resistant to the common psychotropic medications and to the standard therapy with corticosteroids. However, the child responded very well to IVIG treatment, with resolution of the neurological picture. IVIG has been used in pediatric patients with a severe type of autoimmune diseases (SLE included), encephalopathy and immune related motor disorder [3]. In our patient IVIG treatment led to prompt resolution of the neurological clinical signs together with a reduction in antibody pattern of SLE. IVIG is known to also play a neuroprotective role by interfering with the anti-idiotypic network [3-5] and can act through different mechanisms: autoreactive B lymphocyte suppression, neutralization of B cell activation cytokines (reduction of IL-10 and IL-6 secretion), hypoactivation of TLR-9 in B cells, and modulation of the immune response [4,5]. Interestingly, in our patient, we found high levels of antinucleosome antibodies, known to be a better diagnostic marker than anti-dsDNA antibodies for SLE, especially in children. In addition, we found higher levels of neutrotrophins NGF

(nerve growth factor) and BDNF (brain-derived neurotrophic factor) in the CSF of our patient, observed to be deregulated in the serum of SLE patients compared to healthy controls and associated with psychotic symptoms in NPLES.

In conclusion, EBV reactivation can trigger a clinical and laboratory picture of NPLES probably by inflammatory mediators. Therefore, SLE immunological assessment, including antinucleosome antibodies, should be routinely checked in patients with neuropsychiatric signs of EBV reactivation. IVIG should be considered, mainly in children, when standard therapy fails.

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Acknowledgment

We thank Dr. F. Scuderi for her contribution in the laboratory assessment

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