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LETTER TO THE EDITOR

Could coenzyme Q10 supplementation have a role in the treatment of anti-NMDA receptor encephalitis?

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Dear Editor,

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune encephalitis that commonly affects young women with ovarian teratoma [1]. Patients may present with psychotic symptoms, usually preceded by a viral-like prodrome of fever, malaise and headache. Movement disorders, seizures and depressed consciousness are also common [1]. The presence of anti-glutamate receptor (type NMDA) autoantibodies in serum or cerebrospinal fluid is diagnostic, and imaging studies may be normal. Early initiation of immunotherapy and tumor removal (in paraneoplastic cases) can affect prognosis [1]. We report the case of a patient with anti-NMDAR encephalitis who after a poor response to standard immunotherapy, improved shortly after initiating coenzyme Q10 (CoQ10) supplementation.

A 15-year-old female with no relevant history presented with an acute onset of social withdrawal, anterograde amnesia and mutism. Brain magnetic resonance imaging (MRI) was unrevealing. An electroencephalogram showed diffuse wave slowing. She was afebrile. Cerebrospinal fluid (CSF) analysis was normal, culture negative, and there was no evidence of viral infection. Serology for Cytomegalovirus, Epstein-Barr virus and Human Immunodeficiency Virus were negative. Upon suspicion of a psychiatric disease, risperidone was started. However, she developed vomiting, altered mental status and a single generalized tonic–clonic seizure. Valproic acid was started as anticonvulsant. In the next 24 h her condition deteriorated, developing stupor with periods of agitation. All routine laboratory tests were unremarkable, including negative anti-nuclear antibodies and normal c-reactive protein.

Four days later, she developed dystonic seizures, and she persisted with psychiatric manifestations and altered mental status. Two weeks after her initial symptoms, we ordered anti-NMDA antibodies in CSF (ARUP laboratories, Salt Lake City, UT, USA) which were positive at 1:10 (normal values:<1:1). Pelvic ultrasound, and a chest-abdominal-pelvic computed tomography were normal, with no masses. Serum alpha-fetoprotein was normal.

We made the diagnosis of anti-NMDAR encephalitis without tumor and the patient was started on IV gammaglobuliun (0.4 g/kg QD for 5 days) and methylprednisolone (1 g QD for 5 days). After 10 days of presenting no improvement, the patient underwent five sessions of plasmapheresis (1.5 volumes of plasma removed per session) to no avail. We considered starting rituximab, but the cost was prohibitive. We empirically decided to start CoQ10 800 mg/day via nasogastric tube 6 weeks after having started first line therapy, and 4 weeks after initiating plasmapheresis. Within the next 10 days the patient showed remarkable improvement. She was afebrile, oriented, cooperative and started normal enteral feeding. Although a late-onset response to standard immunotherapy could explain our patient's clinical course, the temporal relationship between her improvement and CoQ10 supplementation is intriguing. She was continued on prednisone, 0.5 mg/kg, and discharged 15 days later.

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There are no evidence-based guidelines that support a standard treatment of anti-NMDAR encephalitis. However, an approach of immunotherapy and tumor removal may result in neurological improvement in over 80 % of the patients [2]. Steroids, intravenous immunoglobulin and plasmapheresis are considered the first line treatments, while rituximab and cyclophosphamide are considered as second line treatments [2]. Salvage and/or maintenance treatment includes mycophenolate mofetil, azathioprine and methotrexate therapy. If first line therapy does not result in improvements within 4 weeks, patients are said to be non-responsive [2]. Although we started CoQ10 after this time period, there remains the strong possibility that our observations were the result of a late-onset response, rather than to CoQ10 treatment itself.

The pathogenesis of anti-NMDAR encephalitis is not completely understood, but a predisposition to autoimmunity has been suggested [1, 2]. An external agent (possibly infectious) may interact with a tumor, leading to molecular mimicry and loss of B or T cell tolerance [1, 2]. Immunoglobulin-producing cells move across the blood brain barrier, producing autoantibodies (IgG type) against the NR1 subunits of glutamate NMDAR in the central nervous system [1, 2].

CoQ10 is an essential biological cofactor of the electron transport chain, accepting electrons from complexes I and II. It is a potent antioxidant in mitochondrial lipid membranes [3]. Experimental studies suggest that CoQ10 may be neuroprotective in conditions such as ischemia, atherosclerosis and toxic injury, and it has been proposed as a promising treatment for degenerative neurological disorders [3]. CoQ10 is safe and well tolerated in humans.

There are various immune-modulating pathways that could explain a beneficial effect of CoQ10 over anti-NMDAR encephalitis. In human studies CoQ10 administration resulted in increases in serum values of IgG, T4-lymphocytes and the ratio T4/T8 lymphocytes [4]. In autoimmune disorders such as systemic lupus erythematous, mitochondrial transmembrane potential alterations lead to increased spontaneous T cell apoptosis, reduced activation-induced apoptosis, reactive oxygen species production and expression of other essential mediators of autoimmunity and B cell activation [5]. However, these general mechanisms do not completely parallel the pathophysiological processes associated with anti-NMDAR encephalitis, so a precise cause–effect relationship cannot be ascertained.

The adverse effects and cost of immunosuppressive therapies, coupled with safety associated with CoQ10, make further studies warranted. Although highly speculative, we suggest that CoQ10 could have had a beneficial role in our case through lymphocyte regulation, anti-inflammatory and antioxidant effects. However, further studies would be required to confirm this hypothesis. Finally, CoQ10 should never substitute standard immunosuppressive treatment but only be considered as an adjunct in non-responsive patients such as ours.

Conflict of interest The authors declare no conflict of interest.

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