Chronic urticaria in myasthenia gravis patients – More than occasional coexistence?

To the Editor,

Chronic idiopathic urticaria (CIU) is characterised by transient cutaneous wheals occurring daily or almost daily for more than six weeks. The pathogenic mechanism of more than 65% of patients with CIU remains unknown.[1] In these patients mast cell dysfunction or local activating factors should be taken into account.[2] The coexistence of CIU with autoimmunity is relatively well proven.[3] This phenomenon has mainly been connected with thyroid abnormality although other associations have also been reported. Myasthenia gravis is defined as an organ specific, autoantibody mediated and T-cell dependent human autoimmune disease.[4] In myasthenia patients, despite characteristic clinical features, there are numerous immunological abnormalities described, such as activation of T and B lymphocytes and epithelial cells. One of the characteristic features is anti-acetylcholine receptor antibodies production as well as the ability of cultured thymic lymphocytes to proliferate in the presence of acetylcholine receptors (AChRs).[5] It is still a matter of debate whether AChR-like molecules can be expressed on the surface of other cells and trigger autosensitisation reactions or autosensitisation of lymphocytes is the primary process which takes place initially in the thymus.

Despite the variety of diagnostic procedures, the aetiology of many chronic urticaria cases remains unknown and the reason for further investigation is to find the potential comorbidities which may influence the course of urticaria. In the present study we describe two cases of chronic urticaria and myasthenia coexistence.

Case 1

A 67-year-old man came under our observation reporting recurrent severe episodes of generalised urticaria and tongue angio-oedema for five years. Skin changes were localised mainly on his feet, hands and face, less often on the trunk and appeared spontaneously or/and a few hours after pressure – the diagnosis of delayed pressure urticaria was established according to current guidelines.[6] Three years earlier the diagnosis of type 2 diabetes had been established and treatment with gliclazide was initiated. Five years before the present hospitalisation the diagnosis of myasthenia gravis had been established (untreated and asymptomatic during our observation). Basic laboratory findings were not specific with negative antinuclear antibodies (ANA). Anti-SM, anti-Jo1, anti-dsDNA (double-stranded-DNA) and anti-Scl-70 were negative as well. Complement parameters were normal.

Case 2

A 54-year-old woman was admitted to the hospital because of recurrent severe angio-oedema and urticaria requiring numerous unscheduled medical interventions. She also reported symptoms of delayed pressure urticaria. The symptoms occurred six months before hospitalisation. The patient suffered from arterial hypertension, and underwent twice (three years before) myocardial infarction and coronary angioplasty. Four years before the present hospitalisation the diagnosis of myasthenia had been established and the patient had undergone thymectomy. Myasthenia was effectively treated with mestinon. No significant abnormalities were found in routine laboratory parameters. Serum levels of IgG, IgM and IgA were normal, and complement parameters were unremarkable. ANA, ANCA, anti-SM, anti-Jo1, anti-dsDNA and anti-Scl-70 were negative.

Autoimmunity in CIU with no doubt plays an important role. It has been suggested that 30–40% cases of CIU have in fact an autoimmune background.[3] The autoimmune reactions in chronic thyroiditis and their potential role as a trigger factor in CIU have already been widely discussed and described.[7] The relationship between CIU and autoimmune diseases may suggest that the myasthenia of our patients was not merely a coincidence but there is a pathological link between these two diseases. Both described cases of severe urticaria were preceded by myasthenia which is closely connected with excessive autoantibodies production. In about 80% of myasthenia gravis cases the disease is mediated by antibodies against the nicotinic AChR. These antibodies decrease the number of functional AChRs at the muscle fibre endplate by increasing their degradation and turnover. Additionally, they induce complement-mediated damage to muscle fibres, and block acetylcholine binding to the receptor. In Kageyama-Yahara et al.[8] study nicotinic AChRs were proved to be expressed on mast cells presenting inhibitory effect on mast cell degranulation. As a result, nicotinic AChRs are involved in the negative regulation of mast cell activation with an anti-inflammatory effect.[8] Interestingly, agonists of nicotinic AChRs were supposed to have a therapeutic effect on a murine model of food allergy.[9] The above-mentioned mechanism is particularly interesting in the light of symptoms of delayed pressure urticaria in both subjects described in our study.

There are only a few reports on the coincidence of chronic urticaria and myasthenia gravis – all in distant studies. One of the reports comes from 1977[10] and concerned urticaria found in a patient with myasthenia and SLE. There were suggestions that myasthenia may antedate SLE, because thymus histology in SLE patients shows germinal centres similar to those seen in myasthenia. However, no benefits after thymectomy were shown in SLE cases unlike in myasthenia patients.[10]

To the best of our knowledge in the current literature there are no descriptions of chronic urticaria associated with myasthenia. In our opinion the coexistence of chronic urticaria and myasthenia should be more deeply explored, particularly in the light of the possible role of AChRs in mast cell activation.

Ethical disclosures

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

Conflict of interest

The authors have no conflict of interest to declare

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Epstein–Barr virus infection triggering a haemophagocytic syndrome

To the Editor,

The disease spectrum that can be triggered by the Epstein–Barr Virus (EBV) is very wide, from infectious mononucleosis[1] to more serious entities such as chronic active EBV infection, haemophagocytic lymphohistiocytosis (HLH), the X-linked lymphoproliferative disease and other lymphoproliferative disorders such as T, B and NK lymphomas.[1] With the exception of infectious mononucleosis, these other medical conditions should always arise suspicion of an underlying defect of immunity.

HLH is a clinical syndrome that occurs due to an exaggerated inflammatory reaction as a result of an inadequate response of the immune system.[2] The term haemophagocytosis describes the pathognomonic findings of activated macrophages surrounding erythrocytes, leukocytes, platelets and their precursors. Clinically, HLH is characterised by prolonged fever, pancytopenia, hepatosplenomegaly, and haemophagocytosis in bone marrow, liver, lymph nodes and central nervous system.[2] These events constitute the clinical and laboratory criteria used for HLH diagnosis.[2] HLH was initially thought to be a sporadic syndrome caused by a neoplastic proliferation of histiocytes.[3] Subsequently, familial cases were described, which are currently known as Familial Haemophagocytic Lymphohistiocytosis (FHL). The relationship of HLH with viral infections, and other microorganisms has been demonstrated over time.[1,2,4] Currently the incidence of HLH worldwide is 1.2 cases per million persons per year.[2,5] HLH is divided into two forms: primary or familial, and secondary or acquired. The primary form includes the FHL, in which HLH is the only clinical manifestation of the genetic defect. FHL presents in children under one year of age in 70% of the cases, and has an incidence of 1/1 million newborns per year.[2] The primary form also includes a syndromic form in which the manifestations of haemophagocytosis are associated with other clinical features such as partial albinism (Chédiak-Higashi and Griscelli syndromes) and lymphoproliferation (X-linked lymphoproliferative disease).[2] The acquired form of HLH can occur at all ages. It was initially described in the context of viral infections but has now been linked to many other infections such as fungi, bacteria and parasites (leishmaniasis in particular).[2,6] Also, HLH can occur in the context of autoimmune diseases such as systemic lupus erythematosus, juvenile idiopathic arthritis or Kawasaki disease.[2] In fact, any intense stimulation of cellular immunity (infection, rheumatism, tumour) could virtually trigger a secondary form of HLH.

A girl aged 24 months complained of fever lasting for 20 days, associated with suppurative sore throat, generalised lymphadenopathy and hepatosplenomegaly. She was diagnosed of infectious mononucleosis, with a viral load for EBV of 6350 copies/ml. There was no relevant personal or family history. Due to persistent fever and malaise, she was admitted to hospital. Blood tests revealed panhypogammaglobulinaemia at the expense of IgG (3305 mg/l, normal value (NV): 4350–11,200 mg/l), associated with low IgA and IgM, along with B cell lymphopenia and an expansion of CD8+ lymphocytes. Intravenous acyclovir and immunoglobulin replacement therapy were