

Paraneoplastic Neurological Syndromes: A Condition of Increasing Recognition

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In this issue of the *Israel Medical Association Journal (IMAJ)*, Boniel and co-authors [1] describe a 4 year old girl presenting with severe relapsing involuntary movements and personality changes due to encephalitis. Although the patient did not present with typical eye involvements, she was suspected of having *opsoclonus-myoclonus-ataxia (OMA)*. She was treated with a synthetic adrenocorticotrophic hormone (ACTH)-analogue, steroids, and intravenous immunoglobulins. Eventually she required maintenance therapy with azathioprine.

Serological testing detected persistent anti-Ma2/Ta antibodies as well as anti-nuclear antibody, anti-dsDNS, and anti-Sc170 antibodies, while sera levels declined in further tests. Of interest, in the case presented by Boniel, each relapse appeared after a febrile disease or strenuous physical activity.

Autoimmune-neuropsychiatric disorders, which may be associated with specific auto-antibodies and/or cancer, are termed collectively as paraneoplastic neurological syndromes (PNS). The PNS are a rare group of diseases (diagnosed in approximately 1% of cancer patients) that can affect any part of the central and peripheral nervous systems, as well as the neuromuscular system. They can be divided into two

main categories according to the location of the antibodies. The first group is known as the 'classical' paraneoplastic group (with onconeural antibodies). In this group, the antibodies are directed against intracellular neuronal proteins, such as anti-Hu, Yo, RI, CV2, amphiphysin, Ma1, and Ma2/Ta. The autoantibodies are considered to be epiphenomena, not involved directly in the pathogenesis, while the inflammation is mainly mediated by cytotoxic T cells [2]. This group is related to cancers in 50–60% of positive tests. It is rare for these antibodies to appear in individuals under 18 years of age, and response to immunosuppressive treatment is weak.

In the second group, known as autoimmune encephalitis (AE), auto-antibodies are directed against neural surface antigens or synaptic proteins including receptors, such as NMDA, AMPA, LGI1, CASPR2, and GABAR. These antibodies have a direct pathogenic effect on their target antigens [3]. Cancer relation varies according to antibody [4] and in some cases a genetic predisposition is present [5]. This group affects all ages, including children, and usually responds well to immunosuppressive therapy [6].

The PNS are a relatively newly recognized disorder, and awareness should be increased for clinicians, especially psychiatrists. It has been suggested that a certain percentage of psychiatric patients may actually experience an autoimmune-mediated central nervous system disorder, such as neuropsychiatric lupus or AE [7]. Herken and colleagues [8] reviewed the clinical signs that should prompt evaluation of AE in psychiatric patients. The signs that their group detected included: cerebrospi-

nal fluid lymphocytic pleocytosis without evidence of infection, epileptic seizures, faciobrachial dystonic seizures, suspicion of malignant neuroleptic syndrome, magnetic resonance imaging abnormalities (mesiotemporal hyperintensities, atrophy pattern), or electroencephalography abnormalities (slowing, epileptic activity, or extreme delta brush). Other clinical signs that should raise suspicion of an autoimmune etiology in a psychiatric patient include decreased levels of consciousness, abnormal postures or movements, autonomic instability, focal neurological deficits, aphasia or dysarthria, rapid progression of psychosis despite therapy, hyponatremia, catatonia, headache, and the presence of other autoimmune diseases.

As mentioned earlier, the anti-Ma2/Ta antibody is a 'classical' paraneoplastic antibody. Its presence was brought to attention in a case series by Voltz and co-authors [9] who described 13 male patients with testicular cancer and brain stem and/or limbic encephalitis in which 10 had serum and cerebrospinal fluid antibodies to a 40 kD neuronal protein. This protein, which they called Ma2, was not found in the serum of 344 control subjects. Additional studies revealed that Ma2 was selectively expressed by normal brain tissue and by the testicular tumors of the patients. In some cases in which a rigorous cancer workup is unremarkable, orchiectomy is required to reveal microscopic testicular malignancy [10]. Anti-Ma2 PNS is also found in females in up to 30% of reported cases, in association with several cancer types [11]. In the case presented in this issue of *IMAJ* by Boniel and colleagues [1], anti-Ma2/Ta antibodies were not associated with malignancy up to date. The Ma2 has

some similarity with the Ma1, a protein that is associated with other paraneoplastic neurologic syndromes, particularly brainstem and cerebellar dysfunction. Patients with anti-Ma2 antibodies often develop an encephalitis that is different from 'classical' limbic encephalitis, such as that expected in anti-NMDAR-positive patients. Ma2-associated encephalitis involves not only limbic but also diencephalic or brainstem dysfunction, as well as narcoleptic-related symptoms, eye movement abnormalities, or extra-pyramidal symptoms [12]. Ma2 antibodies are rarely present in children [13], and the patients respond better to immunosuppressive therapy than other well-characterized PNS.

CONCLUSIONS

OMA is a rare syndrome, which is usually present only in young children. It causes opsoclonus (spontaneous, arrhythmic, conjugate saccades occurring in all directions) myoclonus (brief, involuntary movements) with or without ataxia, irritability, and sleep disturbance. The onset of OMA is usually abrupt and often severe; however, the disease may become chronic. OMA could be related to tumors (e.g., neuroblastomas) [14] or follow a viral infections (Epstein-Barr virus, coxsackievirus B, influenza, human immunodeficiency virus, or hepatitis C) or bacterial infections (streptococcal, Lyme disease, or mycoplasma) [15,16]. The treatment includes an ACTH analogue, systemic corticosteroids, intravenous immunoglobulin or rituximab [17]. Children with paraneoplastic OMS have a higher frequency of paraneoplastic antibodies (such as anti-Hu antibodies);

however, there is no specific marker or autoantibody.

The association between OMA and anti-Ma2 is extremely rare, and to the best of our knowledge has only been described in the literature in an 8 year old child [18] and in two adults. The first was an 63 year old man with opsoclonus and cerebellar ataxia without myoclonus, pyramidal signs or a behavioral disorders, which responded to chemotherapy and immunosuppression [19]. The other was a male patient with opsoclonus, limbic encephalitis, and gastric adenocarcinoma [20].

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Capsule

Better broadly neutralizing antibodies by sialization

Certain individuals infected with human immunodeficiency virus (HIV), so-called neutralizers, generate broadly neutralizing antibodies more efficiently than non-neutralizers. Lofano and colleagues compared HIV-specific antibodies isolated from neutralizers and non-neutralizers. They found sialylation of the Fc domain to be higher in neutralizers. The authors generated sialylated and nonsialylated isoforms of an HIV gp120-specific

antibody. Sialylation enhanced the deposition of antigen in B cell follicles in a complement-dependent manner. Besides stressing the importance of the Fc domain in regulating antibody functions, the study also highlights the role of the complement pathway in driving humoral immunity.

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