

## Autoimmune Dementia: Key Points for Diagnosis and Management for an Underestimated Clinical Disorder

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Autoimmune neurology is a rapidly emerging new subspecialty that encompasses the diagnosis and treatment of neurologic disorders with an autoimmune, paraneoplastic or not basis. Many disorders of the central nervous system (CNS) previously considered neurodegenerative and untreatable - such as dementia - are now recognized as having a possible autoimmune cause, while occult cancer accompaniment is not uncommon.

Autoimmune dementia is often not taken into account in the differential diagnosis and usually its presence is underestimated. The general term "Dementia" describes a group of symptoms, which may include memory disorders, mental deficits and changes in mood and communication. Although Alzheimer's Disease, Frontotemporal dementia and Creutzfeldt-Jakob Disease (CJD) are among the most recognized forms of dementia with specific characteristics, sometimes their overlapping features, are similar to those of non-neurodegenerative dementia that is observed in autoimmune diseases.

Even after thorough investigation and evaluation to exclude infections, neoplasms, metabolic or endocrine disorders and possible side effects of any given medication, autoimmune dementia is often not taken into account in the differential diagnosis when cognitive decline is observed in patients, especially in the absence of delirium. This makes the prognosis of the patient unfavorable, especially because the improvement and reversal of symptoms could be achieved through immunotherapy. Features that should prompt the clinician to consider an autoimmune cause for patients with rapid-onset cognitive impairment or unexplained dementia include: suspicious clinical features (subacute onset of symptoms, rapidly progressive course or fluctuating symptoms), personal or family history of autoimmune disease, history of malignancy, smoking, evidence of CNS inflammation from cerebral spinal fluid examination or magnetic resonance imaging (MRI), the presence of one or multiple neural autoantibodies and the potentially therapeutic response to immunotherapy [1-5].

Clinicians should acquire familiarity about a variety of neurological syndromes or autoimmune diseases which need to be differentiated, because they could affect CNS and provoke cognitive decline or dementia like symptoms. The range of possible diagnosis is continually expanding, with the terms of Limbic encephalitis (LE) and of rapidly progressive dementias to be the most used in describing an underlying immune disorder. Included among rapidly progressive dementias is CJD, a relatively untreatable neurodegenerative disease. The clinical symptoms of LE include subacute development of short-term memory loss, complex partial, generalized tonic-clonic or other seizure types, behavioral abnormalities and confusion. Morvan's syndrome, a subtype of anti-VGKC (voltage gated potassium channels) syndromes, is also an immune-mediated disorder of either paraneoplastic or autoimmune etiology. Patients with Morvan's syndrome not only have peripheral (neuromyotonia) but also CNS symptoms (personality changes, hallucinations, sleep disturbances, spatial and temporal disorientation, memory problems and confusion) [1,6].

Other non-paraneoplastic, autoimmune diseases or syndromes, that could affect CNS and provoke among others, dementia like symptoms include: Rasmussen's encephalitis, steroid-responsive encephalopathy associated with Hashimoto's thyroiditis, Neuro-Behçet's syndrome, Neuro-Sjögren's syndrome, Susac's syndrome, neurosarcoidosis, systemic lupus erythematosus, anti-glutamic acid decarboxylase antibody syndrome (anti-GAD) and gluten-sensitivity dementia [1,6].

However there is mounting evidence that specific bacterial, fungal and viral infections could play an active role in the etiology of neurodegenerative and autoimmune illnesses, probably via the newly discovered lymphatic system of CNS or the neurotropism of certain microbial pathogens, such as: herpes simplex virus type 1 (HSV1), JC virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), chlamydia pneumoniae, several types of spirochaete (*treponema pallidum*, *borrelia burgdorferi*), *toxoplasma gondii* (toxoplasmosis), tapeworm infection (cysticercosis) and cryptococcus. It is essential to consider all the aforementioned infections in the differential diagnosis of any patient with unexplained dementia [1].

The development and widespread availability of neural antibody marker testing and their use in daily clinical practice helps in early recognition of cognitive disorders with an autoimmune context, providing not only better management of patients, but also better prognosis. The increasing complexity of neural antibody marker testing requires higher-level knowledge about how to recognize their limitations and how to interpret their presence. The neurological associations of neural autoantibodies tend to be diverse and multifocal, although certain associations with specific syndromes may apply.

Neural autoantibodies presence should raise suspicion for a paraneoplastic etiology and a targeted oncologic evaluation should follow, ideally with paired samples of serum and cerebrospinal fluid. MRI scans, electroencephalogram, functional imaging and neuropsychological evaluations could provide more objective evidence of neurologic dysfunction, as a measure of monitoring response to immunotherapy. Seronegativity for all currently recognized autoantibody markers of neurological autoimmunity does not exclude the diagnosis of autoimmune dementia or cancer in a patient with a subacute neurological presentation [1,7-9].

Surveillance is needed when limbic encephalitis is suspected in a child with sub-acute onset of psychiatric symptoms - with or without associated tumor - despite normal initial brain scan. Diagnosing anti-mGluR5 encephalitis (Ophelia syndrome) may lead to potentially highly effective treatment option and may anticipate the diagnosis of a cancer. It is important to recognize this complex neuropsychiatric syndrome, which usually manifests with short-term or progressive memory loss, personality changes and psychomotor agitation among others, because it can affect young individuals and is reversible in early diagnosis [1,10,11].

Treatment of autoimmune dementias still remains empirical. Nonetheless, the clinical response is best if treated early, so a trial of immunotherapy should be considered in the correct clinical context, even in the absence of identified neural antibodies. If an associated tumor is found, its resection optimizes the neurological outcome. A favorable response to treatment supports the diagnosis of autoimmune dementia, whereas a lack of response should prompt a reevaluation for alternative diagnosis. Beyond treatment of the underlying tumor, first-line immunotherapy could include the use of: corticosteroids, IV immunoglobulin (IVIG) and plasma exchange. Observational studies show that, second-line treatment results in better functional outcomes and lower relapse rates with easy to handle adverse effects. The decision to initiate second-line immunotherapy is made with consideration of the disease severity, response to the first-line immunotherapy, presence of relapse and other clinical conditions. Maintenance immunotherapy is usually recommended in order to maximize therapeutic gain with the highest functional state possible and to attain if possible complete remission in those at risk for relapse [1,12-14].

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