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REVIEW

Anti-neuronal autoantibodies: Current diagnostic challenges

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Abstract
The spectrum of neurological autoimmune diseases has expanded substantially in the last 15 years due to the discovery of new anti-neuronal antibodies. There are at present numerous technical challenges for developing and improving standardized serological test systems for the detection of these autoantibodies, some of which occur very rarely. In particular, the determination of autoantibodies against complex cell surface structures generally requires authentically presented target antigens. Finally, research into syndrome associations benefits from multiplex analyses and accelerates the understanding of the complex autoimmune processes, forming an important basis for the development of novel therapy concepts.

Contents

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1. Anti-neuronal autoimmunity

The term autoreactive antibodies (=autoantibodies) defines immunoglobulins that can bind specifically to the body's own structures (=autoantigens). The induction of such autoantibodies parallel to the clinical course is currently not completely understood. Events that lead to damage or changes to tissues are most likely involved. These include viral infections, tumor diseases and traumatization. Limited autoreactivity appears to have a purpose in evolutionary terms, for example to effectively defeat viral infections or tissue degeneration. In cases of autoimmune disease, unlimited autoreactivity (loss of immunotolerance) contributes substantially to pathogenesis.

Autoantibodies can be divided into apathogenic and pathogenic antibodies. Apathogenic anti-neuronal antibodies cannot generally bind to the corresponding antigen under *in vivo* conditions. This group includes autoantibodies against intracellular components such as the neurological antigens CV2, Ri, Ta, Ma, Hu and Yo. In contrast, autoantibodies that bind to their autoantigen *in vivo* have in most cases significant pathogenic potential, since they lead to tissue damage or dysfunction of cellular signal transduction mechanisms. Important examples of the latter are autoantibodies against cell surface structures, such as muscular acetylcholine receptors (AChR) or glutamate receptors (type NMDA) (Lancaster and Dalmau, 2012; Moscato et al., 2010).

Paraneoplastic neurological syndromes encompass a special group of autoimmune diseases (Dalmau and Rosenfeld, 2008; Graus et al., 2004; Graus and Dalmau, 2012; Leypoldt et al., 2012). The cause of disease is an immune reaction that is predominantly directed against the tumor tissue. As a result of the predominantly T-cell-mediated tissue damage, the immune system is massively stimulated via the release of intracellular and normally inaccessible autoantigens. A specific humoral autoimmune reactivity is induced and can be exploited as a diagnostically valuable epiphenomenon (Albert et al., 1998; Bien et al., 2012; McKeon and Pittock, 2011; Melzer et al., 2013; Rousseau et al., 2005). Anti-neuronal autoreactivity is frequently generated due to the production of neuronal proteins in ectodermal tumors. The result is a loss of functionality of the particularly sensitive central nervous system. Degenerative changes manifest in the form of massive dysfunctions and for this reason they become clinically conspicuous at an early stage. Therapeutic intervention in these cases consists of searching for and removing the causative tumor in order to eliminate the disease-triggering stimulus (Voltz, 2002). However, a tumor is not detectable in many patients.

If the autoantibodies are directed against intracellular autoantigens (classic paraneoplastic antibodies), it can be assumed that the neuronal tissue damage is initially mediated by T-cells. Consequently, an immunosuppressive therapy, which is aimed at suppressing B-cells, does not usually improve the clinical symptoms. If, in contrast, essentially cell surface structures are the target of the humoral reaction, early immunosuppression and, if applicable, tumor resection is indicated. In these cases substantial recovery is possible (Bien et al., 2012; Dalmau et al., 2011; Lancaster and Dalmau, 2012).

In the last 15 years, various autoantibodies against surface proteins of neuronal cells have been described, some paraneoplastic, others non-paraneoplastic, especially in the area of encephalitides previously classified as idiopathic ("encephalitis of unknown origin"). Examples target glutamate receptors (type NMDA and type AMPA), $GABA_B$ receptors, LGI1, and CASPR2. These autoantibodies exhibit an unexpectedly high prevalence in encephalitis and have led to an intensive search for autoimmune processes in further neurological conditions, as reflected in the large number of recent publications and reviews (Dalmau et al., 2008; Irani et al., 2010a; Lai et al., 2009, 2010; Lancaster et al., 2010, 2011a, 2011b; Vincent et al., 2011; Zuliani et al., 2012). Due to the sometimes very low numbers of reported cases, it has not yet been possible to draw definitive conclusions about the syndrome associations of some of these autoantibodies.

In the group of inflammatory CNS demyelinating autoimmune diseases, autoantibodies against the astrocyte water channel aquaporin-4 (AQP4) allow early differentiation of neuromyelitis optica (NMO) and its limited forms (optic neuritis, longitudinally extensive transverse myelitis) from multiple sclerosis (MS), which is crucial as treatment options differ (Lennon et al., 2004, 2005; Waters et al., 2012). Among the rare cases of anti-AQP4-negative NMO spectrum disorders, there are some with high-titer autoantibodies against myelin oligodendrocyte glycoprotein (MOG), a CNS-specific transmembrane protein localized on oligodendrocytes and on the outermost lamellae of myelin sheaths (Mader et al., 2011; Rostasy et al., 2012, 2013). However, solid immune responses against MOG have also been found in mainly pediatric patients with acute disseminated encephalomyelitis, clinically isolated syndrome or MS (Brilot et al., 2009; Di Pauli et al., 2011; Lalive et al., 2011; Mader et al., 2011; Selter et al., 2010).

Despite strong evidence that MS is an autoimmune disease, an unambigious target of the immune attack has not yet been identified despite intensive research. One of the latest reports demonstrated autoantibodies against the inward rectifying potassium channel KIR4.1 in 47% of MS patients – without association to their clinical subtype – and in only 0–1% of controls (Srivastava et al., 2012). The relevance of this finding, however, is controversially discussed and still needs to be confirmed by independent data. Further candidate autoantigens in MS include components of the CNS myelin, e.g., MOG, myelin binding protein, myelin associated glycoprotein (Baig et al., 1991; Di Pauli et al., 2011; Quintana et al., 2012; Wajgt and Gorny, 1983), the axoglial proteins neurofascin and contactin-2 (Derfuss et al., 2009, 2010; Mathey et al., 2007), axonal cytoskeletal proteins (neurofilaments) (Ehling et al., 2004; Fialova et al., 2013; Silber et al., 2002), gangliosides (Sadatipour et al., 1998), and others (Quintana et al., 2012; Vyshkina and Kalman, 2008). The corresponding autoantibodies are probably markers for demyelination and axonal damage,