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Review Article

ANTIBODIES IN NEUROLOGICAL DISORDERS

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Abstract: Detection of specific autoantibodies to neural targets has resulted in a better understanding of autoimmune neurological disorders. Neural antibodies have led to categorization of neurological diseases disease as autoimmune which were previously thought to result from infectiousor psychogenic causes or considered idiopathic. Antibodies directed to intracellular antigens are commonly associated with cancer and are poorly responsive to immunotherapy. Cell surface antibodies on the other hand are directly pathogenic and mediate the neurological disease. This review summarizes the neurological disorders, antigenic targets and pathogenic mechanisms of most common neural antibodies.

Keywords: Neurological disorders,

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We dedicate this article to Dr P.D. Gupta whose passion for research and love for writing has been a constant source of inspiration to us. His words of wisdom have touched so many lives. On his 85th birthday, we wish him many more years of good health as he continues to spread happiness to those around him.

INTRODUCTION

Autoantibodies that target neuronal antigens were initially recognized in 1960 by Dr. Wilkinson and Dr. Zeromski in patients with sensory neuropathy and bronchial carcinoma [1]. Subsequently many antibodies associated with neurological disorders have been discovered. Neural-specific antibodies serve as biomarkers for neurological disorders that can affect any axis in the nervous system.

The target antigens of these antibodies can be either intracellular or plasma membrane proteins. Recognition of these antigens and antibodies has helped us to elucidate the pathogenesis of various autoimmune neurological disorders. This review discusses the types of antibodies and their associated neurological diseases.

Intracellular antigens: These antigens are found in the nucleus, nucleolus and cytoplasm of the neuronal cells. These antibodies are commonly found in association with cancers. They are directed against the antigens that are expressed in both the tumor and neural tissue.Since these antigens are intracellular the antibodies are not directly pathogenic. This has been proved in animal models as well [2]. Instead, a T cell mediated process is the driving force in these disorders. Immunohistopathological studies of patients with paraneoplastic neurological syndromes (PNS) have shown CD3+ and CD8+ T-lymphocyte infiltrates in brain or dorsal root ganglia. This supports cytotoxic T-cell drive the pathogenesis in these diseases [3]. Response to therapy is usually poor in neurological disorders associated with these autoantibodies, due to irreversible neuronal death.

Some of the most common antibodies directed against the intracellular antigen are discussed below.

1. **Anti neuronal nuclear antibody type 1:** antibodies:These antibodies are directed against the Hu antigens which is a RNA-binding protein. It is involved in cell-cycle regulation and cell development [4]. These antibodies are most commonly found in small cell lung cancer (SCLC). Interestingly, only 20% of patients with SCLC have serum Hu antibodies and less than 0.01% of patients develop PNS. The clinical picture includes – sensory neuropathy, cerebellitis, limbic encephalitis, autonomic dysfunction and/or brainstem encephalitis.

2. **Anti neuronal nuclear antibody type 2 :** The antigen of this type of antibody is the NOVA family of RNA-binding proteins (NOVA-1, 55 kDa, and NOVA-2, 80 kDa[5]. They play a role in alternative splicing of neuronal-transcripts encoding synaptic proteins. ANNA-2 antibodies were first reported in women who had opsoclonus–myoclonus syndrome and cerebellar ataxia with breast cancer. Brainstem syndromes and cerebellar syndromes are the most common neurological presentations. Laryngospasm and/or jaw dystonia has been reported in up to 25% of ANNA-2 paraneoplastic encephalitis patients [6].

3. **Purkinje cell antibody type 1:** The antigen for Purkinje cell cytoplasmic type 1 (PCA-1/anti-Yo) is the 52 kDa cerebellar degeneration-related protein 2 (cdr2)[7]. It downregulates DNA transcription through inhibition of c-Myc. However, in a recent study it was shown that these antibodies bind to CDR2 ligand and not CDR2. Paraneoplastic cerebellar degeneration (PCD) is the most common clinical syndrome associated with PCA-1 antibodies. It occurs mostly in women with gynecological malignancies [9]. However, a few paraneoplastic cases in men with breast or cholangiocarcinoma have also been reported [10].

4. **Collapsin response-mediator protein-5 antibody:** Collapsin response-mediator protein 5 (CRMP-5)-IgG is a 62 kDa phosphoprotein involved in axonal guidance in the collapsin response-mediator protein 5 (CRMP-5)-IgG is a 62 kDa phosphoprotein involved in axonal guidance in the developing nervous system [11]. CRMP-5-IgG is one of the most common paraneoplastic antibodies. It is typically associated with SCLC and thymoma. Neurological manifestations include radiculoneuropathies, autonomic neuropathy, myelopathy,optic neuropathy combined with retinopathy [12].

5. **Ma1/MA2 Antibody:** Ma1 and Ma2 antibodies are directed against homologous. neuronal nuclear proteins (40 and 42 kDa) with speculated involvement in RNA transcription and apoptosis regulation (23). The neurological disorders associated with Anti Ma1/Ma2 affect mesial temporal lobes, diencephalon, brainstem, and cerebellum [13].

6. **Kelch-like protein 11 (KLHL11) Antibody:** These antibodies were first discovered in 2019.

They usually present with rhombencephalitis. Tinnitus and hearing loss are common findings and can precede encephalitis by weeks to months. Most common tumor associated is testicular germ cell tumors, primarily seminoma [3].

Cell Surface and synaptic antigens: The antibodies to these are directed against the antigens that are present on the cell surface and synapses. They differ from antibodies against the intracellular antigen in the way that they are directly pathogenic. There are various mechanisms by which they exert their pathogenic effect. Since they are directly pathogenic therapies that deplete their level result in disease resolution. Hence, these neurological have been found to have better prognosis. The following section describes the most common cell surface antibodies, their pathogenic mechanisms and disease manifestations.

1. **Aquaporin 4 antibodies:** Aquaporin 4 (AQP 4) the antigenic target of AQP4 antibodies is concentrated on astrocytic end-feet. It is also found in skeletal muscle, stomach, lung, kidney, inner ear, retina and olfactory epithelium [14]. AQP 4 antibodies were first discovered in 2004 by Lennon and colleagues. Recognition of AQP4 antibodies led to distinction of neuromyelitis optica (NMO) from Multiple Sclerosis. They induce complement dependent cytotoxicity and hence complement inhibitors are very effective in this disorder. NMO is typically characterized by optic neuritis and myelitis. However, over the years the spectrum has expanded and now includes area postrema, cerebral, diencephalic and brainstem syndromes [15].

2. **N-methyl-D-aspartate-receptor (NMDA-R) antibodies:** NR1 subunit of the NMDAR—is the primary target of the antibodies against the NMDA receptor. NMDA receptor is involved in synaptic plasticity, learning and memory. They were first discovered in 2007 by Josep Dalmau in women with ovarian teratoma [16]. They act by receptor cross-linking, internalization and degradation, thus reducing the number of NMDARs on the neuronal surface [17]. It is usually seen in young women presenting with subacute neuropsychiatric manifestations, seizures, encephalopathy, dyskinesias, and autonomic dysfunction. Newer cohorts have expanded its spectrum and it is also seen in children women without teratoma, and men as well [18].

3. **Leucine-rich glioma-inactivated protein 1 (LGI1) Antibodies:** These antibodies target the LGI1 protein which is a 64 kDa, protein expressed mainly in the hippocampus and neocortex. LGI1 antibodies block interaction with LGI1 and ADAM22/23 resulting in decreased AMPA receptors on the cell surface [19]. It commonly presents with epilepsy mostly faciobrachial dystonic seizures, limbic encephalitis, hyponatraemia, autonomic dysfunction and sleep disturbances [20].

4. **Contactin-associated protein 2 (CASPR2) Antibodies:** CASPR2 a 148 kDa protein is predominantly expressed in the juxtaparanodal region of myelinated axons in the brain and peripheral nervous system [21].CASPR 2 antibodies are associated with thymomas in about 20% of cases. However, other tumors have been reported such as melanoma have been reported. CASPR 2 antibody mediated disease manifests as Morvan's syndrome, peripheral nerve hyperexcitability, cerebellar dysfunction and limbic encephalitis [20]. PNS manifestations can either-precede or follow the CNS manifestations.

5. **Gamma-Aminobutyric acid A receptor (GABAAR) Antibodies:** GABAAR are ionotropic ion channels that allow the influx of chloride ions and lead to synaptic inhibition[14]. The antibodies lead to decreased expression of GABAa receptor ion the cell surface. GABA – A receptor encephalitis presents with seizures, status epilepticus and catatonia. They are not commonly associated with tumors (<20%) [22].

6. **Gamma-Aminobutyric and acid B receptor (GABABR) Antibodies:** GABABRs are G-protein coupled receptors which regulate the presynaptic inhibition via second messenger systems. These antibodies block receptor signaling by blocking the binding of GABA to its receptor [19]. GABA-B-R encephalitis presents with refra-ctory seizures and limbic encephalitis. GABA-B-R antibodies have been associated with malignancy in 50-60% of cases, usually small-cell lung cancer [23].

7. **Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor Antibodies:** AMPARs are ionotropic glutamate receptors that are important for excitatory neurotransmission. GluR1 and GluR2 subunits of the receptor are

targeted by the AMPAR antibodies. AMPA IgG leads to limbic encephalitis, psychiatric symptoms and sleep disturbances. They are commonly associated with tumours such as SCLC, breast, ovary and thymoma [24].

8. **Intracellular synaptic antigens:** GAD65 and amphiphysin are intracellular synaptic antigens. These antigens during synaptic fusion can be exposed to antibodies. Therefore, antibodies to these two antigens can be pathogenic in addition to a T cell mediated damage.

GAD 65 antibodies lead to stiff person syndrome (SPS). Other syndromes associated with this antibody include cerebellar ataxia, limbic encephalitis and epilepsy. These antibodies have been found to decrease the synthesis of GABA in vitro [25]. Anti Amphiphysin antibodies also lead to SPS but it is usually seen in setting of breast cancer. The clinical phenotype also includes neuropathies, ataxia and limbic encephalitis. [26]. These antibodies alter the GABAergic transmission [27].

CONCLUSION

The discovery of antibodies and their antigenic targets has enhanced our understanding of autoimmune neurological disorders. These antibodies serve as biomarkers of various diseases and help us diagnose them. Many of them have been found to be directly pathogenic as well. Cell surface antibodies respond better to immune therapy unlike intracellular antibodies which are poorly responsive to immune therapy.

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