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PEARLS OF LABORATORY MEDICINE

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TITLE: Autoimmune Neurology: Paraneoplastic Disorders and Beyond

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Slide 1:

Hello, my name is Andrew McKeon. I am a director of The Neuroimmunology Laboratory, and Professor of Neurology, and Laboratory Medicine and Pathology at Mayo Clinic, Rochester Minnesota. Welcome to this Pearl of Laboratory Medicine on "Autoimmune Neurology: Paraneoplastic Disorders and Beyond."

Slide 2:

Autoimmune Neurology has been an emerging subspecialty in clinical and laboratory medicine that is now mainstream. Neural antibody biomarker testing is now commonly undertaken by neurologists and other providers. Why? Simply put, for any patient with a rapidly progressive neurological disorder the question on the provider's mind is: 'is this treatable?'. Many autoimmune neurological disorders, have an occult early stage neoplasm associated with the neurological presentation. The neurological symptoms themselves in many instances are responsive to immune therapy such as corticosteroids, plasma exchange, intravenous immune globulin, cytotoxic agents such as cyclophosphamide, or monoclonal antibody therapies, such as rituximab. This 'Clinical Pearl' will provide a bird's eye view of Autoimmune Neurology: definition, clinical presentations and testing.

Slide 3:

By way of definition, autoimmune neurological disorders include any disorder of the nervous system whereby dysfunction is caused by the immune system. These are classified as organ specific autoimmune diseases. Well-known examples of non-neurological organ specific autoimmune disease include Hashimoto thyroiditis and rheumatoid arthritis.

More and more, autoimmune neurological disorders are being unified by the presence of a neural antigens specific autoantibody in serum or cerebrospinal fluid, also known as CSF. The localization of these targets can include the plasma membrane of neurons or glial cells (astrocytes, and oligodendrocytes), or intracellular targets in the nucleus, cytoplasm or nucleus. Broadly speaking, the initiating factor may be cancer or infection. The neurological disorders are known as paraneoplastic or parainfectious respectively. While some patients may have an autoimmune predilection through genetic background, otherwise many patients with neurological autoimmunity develop there disorders for reasons yet unknown.

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Generally speaking, most patients with autoimmune neurological disorders present with a subacute onset of symptoms, meaning onset occurring over days to weeks. Progression tends to be rapid. Sometimes patients will report having had spontaneous improvements or remissions, which would be atypical for non-autoimmune degenerative disorders. The clinical course may be fluctuating. While there are classical disorder such as limbic encephalitis, consisting of rapidly progressive cognitive decline, behavioral change, seizures and mood disturbance, there are many patients who present with unusual non-textbook clinical presentations. These can occur for a couple of reasons. Firstly, patients may have a restricted version of the classical phenotype. For example, some patients with limbic encephalitis may just present with seizures. This has led to the concept of autoimmune epilepsy. Secondly, there are other patients who may have a multifocal neurological disorder. Thus there are many potential permutations and combinations. For example, among patients with limbic encephalitis, some may have accompanying spinal cord dysfunction known as myelopathy, or dysfunction of nerves in the peripheral nervous system known as peripheral neuropathy, or perhaps even both.

Slide 5

Some anatomic and neurologic terminology is required to contextualize the utility of different antibody biomarkers in different neurological phenotype based antibody testing profiles. Autoimmune disorders affecting the cerebral cortex could include features of encephalopathy or encephalitis (global brain dysfunction, accompanied by confusion), dementia (impaired cognitive function only) potentially mimicking degenerative diseases such as rapidly progressive Alzheimer disease), or seizures alone. At the level of the visual system, patients could have

inflammation of the optic nerve known as optic neuritis, or could have rapidly progressive nighttime vision loss, autoimmune retinopathy, which could mimic macular degeneration. Movement Disorders include the relatively common autoimmune cerebellar ataxia. There is a pot pourri of other less common autoimmune movement disorders including chorea (dance like movements) which could mimic an untreatable genetic disorder known as Huntington disease. Patients with autoimmune brainstem disorders, known as rhomboencephalopathies, may have problems including eye movement or balance disorders which could potentially mimic Parkinson disease. Patients with spinal cord dysfunction, known as myelopathy, may have sensory loss, pain, limb weakness, and bowel or bladder dysfunction. Common causes include stroke or multiple sclerosis. There are some patients with paraneoplastic or other forms of autoimmune myelopathies that could mimic more common spinal cord disorders. Stiff person syndrome specifically affects the inhibitory interneuronal pathways of the brainstem and spinal cord. The conus medullaris is at the intersection between the central nervous system (above) and peripheral nervous system (below). This can be affected in paraneoplastic myeloneuropathies (both central and peripheral nervous systems involved). At each spinal cord level, there is a sensory component with peripheral sensory nerves carrying electrical signals to the nerve roots via the dorsal horn, and then to the spinal cord, and finally the brain. Autoimmune radiculopathies or neuropathies may be encountered. In the motor system electrical signals are conducted from the brain via the spinal cord to the anterior horn, and then to peripheral motor nerves. Electrical signals are converted to chemical signals at the neuromuscular junction and then transduced to muscle to enable muscle contraction and ultimately produce movement. Autoimmunity can affect both the insulation of the nerve, known as myelin, or the wire itself, known as the axon. When the insulation is affected this is referred to as demyelinating neuropathy, or if the wire is affect, it is referred to as axonal neuropathy. At the neuromuscular junctions or synapses, autoimmunity can produce broadly 1 of 2 disorders: Calcium channels at the presynaptic membrane causing Lambert-Eaton syndrome, or acetylcholine receptors at the postsynaptic membrane causing myasthenia gravis. Autoimmunity of muscle can result in non-inflammatory necrotizing myopathy or inflammatory myositis.

Slide 6

Some neurological presentations are classical, though others more limited or atypical. When trying to build a picture of autoimmunity, it is important for clinical providers to ask in detail about

medical history. Sometimes there is none apparent. However some patients have an autoimmune disease affecting another organ pre dating neurological symptom onset. Examples include Hashimoto thyroiditis, autoimmune diabetes, rheumatoid arthritis, celiac disease, autoimmune adrenal insufficiency known his Addison's disease, or non-organ specific, multi systemic autoimmune connective tissue diseases such as systemic lupus erythematous or mixed connective tissue disease. A cancer history may also be pertinent, particularly if the cancer occurred in the preceding 3 years, though remote cancer history does not exclude the possibility of relevance to the neurological presentation. Smoking history is also important. Small cell carcinomas, or other neuroendocrine lineage neoplasms are more common among smokers, and are most associated with paraneoplastic neurological symptomatic presentations. It should be pointed out, that patients with paraneoplastic neurological disorders, may present to a neurologist with neurological symptoms, and have a cancer subsequently found. Alternatively, patients who have an established cancer diagnosis, may develop neurological symptoms later on, often during treatment. For the oncologist, the question often is could the patient have chemotherapy or radiation therapy related side effects, or a paraneoplastic neurological disorder. There may also be a stroke family history for autoimmune diseases or cancer that may provide clues also. It is also important to ask about recent documented infections, and preceding infectious type symptoms. Results from 1 or more supportive diagnostic tests such as MRI imaging, electroencephalogram, and electromyography may assist in providing objective evidence of specific types of neurological dysfunction.

Slide 7

After considering the history and examination, the provider has established the neurological phenotype, and medical historical factors prompting consideration of an autoimmune cause for neurological symptoms. There may be benefit to testing for non-neural autoantibodies. That is not because these autoantibodies cause neurological disease, but more so positivity may be another clue that helps build the case for an autoimmune cause. Many patients with autoimmune neurologic disease, who have proven treatment responsive, are neural autoantibody negative in serum and CSF. The numbers of these patients is gradually reducing with time, due to discovery of additional new IgG biomarkers. In the spinal fluid, there are more generic inflammatory markers,

such as protein, cell count, IgG index and oligoclonal bands. Though not specific for 1 disease, these may assist in diagnosis of a variety of autoimmune and inflammatory disorders. Neural IgG autoantibodies may be detected in serum, CSF or both. Which specimen types to test is determined by the phenotype at presentation, and the particular analytes pertinent to that phenotype

Slide 8

Using the paradigm of a paraneoplastic disorder, there is an appropriate vigorous immune response against 1 or more neural antigens expressed in tumor cells. That immune response in turn, due to other factors, results in autoimmunity directed against the nervous system. In that context IgGs, which service biomarkers, are generated. The red autoantibodies on the left represent those that are directed against extracellular epitopes of plasma membrane-bound proteins such as ion channels, and receptors. In general, these autoantibodies are considered pathogenic by causing internalization of receptors, and inflammation by activation of the classical complement cascade. In general, many patients with these biomarkers detected have good responses to immunotherapies such as plasma exchange or steroids. On the right, there are the green antibodies, which represent those that are generated in the context of a cytotoxic T-cell mediated response against cytoplasmic, nuclear or nucleolar protein episode worse. In the context of upregulated MHC class 1, these proteins are processed and expressed on the cell surface, and are recognized by T lymphocytes. Autoantibodies generated in that context, are not thought to be pathogenic, but can be equally useful as the red colored pathogenic antibodies as diagnostic biomarkers in the laboratory.

Slide 9:

In the following 2 slides, lists of autoantibodies and recognized cancer associations can be found. On the first of those 2 slides, note the common association of small-cell carcinoma with various neuronal nuclear and cytoplasmic autoantibodies. Thymoma and breast adenocarcinoma are other common neoplastic accompaniments. For most of these autoantibodies, the positive predictive value of a subsequent cancer diagnosis when 1 or more of these autoantibodies are detected is approximate 70%. At the bottom of the table highlighted in yellow, are some more recent discoveries and cancers where pertinent. Historically there

have been 2 nomenclatures, which have the potential to cause confusion. All have initially or ultimately been defined by the antigen protein name. Several also have a name defined by the appearance of autoantibody staining of mouse brain on indirect immunofluorescence assay. An example of this is the classical small cell carcinoma associated autoantibody, with the protein derived name of anti-Hu. Because this autoantibody predominantly stains neuronal nuclei, it is also known as anti-neuronal nuclear autoantibody type 1 (ANNA-1).

Slide 10:

On the 2nd of those 2 slides, note the diverse reported cancer associations. For most of these, except for where highlighted in yellow, the cancer predictive value is low, 20% or less.

Slide 11:

In the diagnostic serology laboratory, autoantibodies can be detected by a variety of different assay methodologies. Different neural autoantibodies may be detected by identifying diagnostic criteria-specific patterns of immunofluorescence on rodent nervous system tissue (bottom left). A specific cytoplasmic staining is produced by Purkinje cell cytoplasmic antibody type 1 (also known as PCA-1 or anti-Yo). A commercial line-blot is demonstrated in the bottom, middle, and cell-based assay, bottom, right. Use varies by autoantibody type, those with specificity for extracellular 3D conformational epitopes, and those reactive with linear intracellular epitopes.

Slide 12

Most current applications of FACS relate to studying cell size and cell surface markers of blood cell populations, for example the evaluation of hematologic malignancy. FACS can also be used to determine the presence or absence of an antibody of interest by studying 2 populations of cells, one transfected with the antigen of interest (in this case aquaporin-4), and the other consisting of untransfected cells.

This is an example of an aquaporin-4-IgG negative serum tested by FACS. In the left panel, the healthy cells are selected by gating a population that does not include any debris. This population is then analyzed for 2 measures demonstrated in the left panel: 1) green fluorescent protein (GFP), on the X axis, which is indicative of expression of aquaporin-4 by the cells, and 2) detection of aquaporin-4 IgG by secondary antibody (Alexa 647) binding to cells, on the Y-axis. In this example, the secondary antibody binds to GFP negative and GFP positive populations in equal measure. Thus, the result is negative.

Slide 13:

In contrast, this is an example of an aquaporin-4-IgG positive serum tested by FACS. In this case the GFP positive and negative populations are not equal, and the increase in secondary antibody signal and hence amount of primary IgG on the cell surface is evident.

Slide 14:

The IgG binding index allows us to express results quantitatively and is the product of dividing the median fluorescence intensity of the GFP positive population by the median intensity of the GFP negative population. As an example the IgG binding index for the negative serum would equal 1.24, and for the positive serum would equal 30.2.

Slide 15:

In the following 4 slides, some examples of autoimmune neurological disease will be reviewed. Each also presents an opportunity to review some testing principles.

Inflammation characteristic of limbic encephalitis is represented radiologically here by this coronal T2 FLAIR image. Below the clinical symptoms, there is a list of limbic encephalitis associated autoantibodies. In my experience, for the most part, the subtleties of an encephalopathy history and examination are poorly predictive of antibody type detected in the laboratory.

Slide 16:

Also, limbic encephalitis, and other non-limbic encephalitides, such as NMDA receptor encephalitis, have overlapping clinical features, and presentations are not always as classical as described in the literature. In addition, some autoantibodies are more readily detected in serum, such as LGI 1 antibody, and others more sensitively and specifically detected in CSF, such as NMDA receptor antibody. Thus, testing of both serum and CSF for a broad profile of all well character autoimmune encephalitis antibodies is recommended. In contrast, patient who presents with painful vision loss and is diagnosed with optic neuritis, only requires 2 autoantibody test currently, MOG and aquaporin-4 IgGs, both in serum. Non expert physician guided antibody test selection generally leads to either overutilization or underutilization of tests.

Slide 17:

Autoimmune cerebellar ataxia, is classically associated with a paraneoplastic cause in women with ovarian or breast cancer. That disorder almost universally has a poor outcome leading to severe irreversible degeneration of the cerebellum, as illustrated here on this sagittal MRI. However, in more recent times other autoantibodies have been identified. These include metabotropic glutamate receptor 1 antibody, and also septin-5 antibody, the latter illustrated in this indirect immunofluorescence figure. Detection of those autoantibodies, less commonly leads to a cancer diagnosis, immunotherapy response frequently occurs, and neurological outcomes may be more

benign. Although these patients present with the same clinical ataxia syndrome, the different autoantibodies in a movement disorders profile, portend different cancer diagnoses, and also different neurological prognoses.

Slide 18:

While the last few slides have focused on central nervous system disease as examples, as illustrated earlier, autoimmunity can affect any level of the nervous system. The antibody tests available are diverse and growing and some are more sensitively and specifically detected in CSF than in serum, or vice versa. Thus neurological phenotype based evaluations are recommended.

Slide 19:

…and are illustrated herein.

Slide 20:

To conclude, autoimmune neurological disorders, are diverse in clinical presentation, but have some features in common such as rapid onset and progression, there may be other clues from the history, clinical examination, and a variety of biomarkers, including neural autoantibody testing in serum and CSF. These disorders are increasingly recognized. Though some are rare, collectively these disorders are sufficiently common in nonselective general neurology and subspecialist practices to warrant consideration. Positivity for 1 more these biomarkers may assist in a targeted search for occult cancer, give support for treating with immunotherapies, and may assist in predicting outcome.

Slide 21:

References

Slide 22:

Disclosures

Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on "Autoimmune Neurology: Paraneoplastic Disorders and Beyond

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