PARANEOPLASTIC DISORDERS CAUSING EYE MOVEMENT ABNORMALITIES

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LEARNING OBJECTIVES
1. To be able to recognize paraneoplastic ocular motility disorders.
2. To know the workup of these patients and the difficulties with diagnosis.
3. To have an idea about categories of treatment for these conditions.

CME QUESTIONS
1. What are the categories of paraneoplastic neurological disorders that are associated with eye movement abnormalities, and which motility disorders may be found?
2. How should a patient be evaluated for paraneoplastic disease?
3. What tests should be ordered on the CSF?

KEY WORDS
1. Paraneoplastic
2. Eye movements
3. Occult cancer

Paraneoplastic neurologic syndromes constitute a heterogeneous group of disorders which are manifestations of an immune response to a tumor. The pathogenesis is incompletely understood, but the body mounts an immune response directed against antigens which are shared between the tumor and normal tissue from the nervous system. Most of the identified antibodies are simply markers for paraneoplastic processes. They are not pathogenic. Including paraneoplastic and non-paraneoplastic autoimmune disease, there are only five disorders where the antibodies are truly causative and these are all disorders of peripheral nerve or the neuromuscular junction. They are:
1. PQ type voltage gated calcium channel antibodies in the Lambert–Eaton Syndrome (LEMS).
2. Acetylcholine receptor antibodies in myasthenia gravis.
3. Voltage gated potassium channel antibodies in neuromyotonia.
4. Ganglionic acetylcholine receptor antibodies in autonomic neuropathy.
5. Recoverin antibody found in carcinoma associated retinopathy.

The first four are not exclusively paraneoplastic as they can be seen without malignancy.

In some cases the presence of paraneoplastic antibodies seems to be associated with a better immune response against the tumor and actually a better overall clinical prognosis.

Paraneoplastic syndromes were at one time considered to be uncommon. With better understanding of what these disorders are, however, the frequency with which they occur is recognized to be more than previously thought. The more common syndromes such as Lambert Eaton Syndrome occur in as many as 3% of patients with small cell lung cancer. Myasthenia affects 15% of all patients with thymoma. For other solid tumors, the incidence is less than 1%. In the peripheral nervous system paraneoplastic disorders affect 5 to 15% of patients with plasma cell dyscrasias.

The paraneoplastic syndromes which cause abnormal eye movements are mostly those that affect the central nervous system with either an encephalomyelitis, cerebellar degeneration, or the syndrome of opsoclonus, myoclonus and ataxia. Other major categories of paraneoplastic disorders include the syndromes which affect the spinal cord and dorsal root ganglia including Stiff-Person Syndrome (with eye movement abnormalities), and the syndromes affecting peripheral nerve and muscle. In the latter, there may be oculomotor weakness, as in paraneoplastic Guillain Barre Syndrome, and, when there is autonomic pathology, pupillary and lacrimal problems may be seen.

Encephalomyelitis consists of involvement of multiple areas of the nervous system, most particularly including the temporal lobes and limbic areas, brain stem, cerebellum, spinal cord, dorsal root ganglia and autonomic nervous system. The distribution of lesions is patchy and varies greatly between patients. The pathology in general is a perivascular and interstitial inflammatory infiltrate of T–cells with gliosis, neuronophagic nodules and neuronal loss. A large majority of patients with encephalomyelitis have anti–Hu (antineuronal or ANNA–1). The most common associated cancer is small cell lung cancer which accounts for 75% of cancers associated with these clinical syndromes. Anti–Hu is particularly associated with myelitis and limbic encephalitis.

Ma2 associated encephalitis is particularly associated with testicular cancer. Patients have limbic, diencephalic and brain stem findings and daytime sleepiness is very common. Eye movement abnormalities, especially vertical gaze palsies, are frequently present and the patient’s eye
movement abnormalities can progress to total external ophthalmoplegia. These eye findings should always prompt consideration of a paraneoplastic disorder, particularly if the findings are not classical for progressive supranuclear palsy. In 34 patients with these findings, 18 were found to have testicular germ cell tumors. In six men with Ma2 antibodies and negative detailed evaluation for malignancy, orchietomy revealed microscopic testicular cancer. These men all were thought to be at risk for testicular cancer because they had testicular enlargement, testicular microcalcifications and/ or cryptorchidism. Some patients have midbrain involvement with a Parkinsonian syndrome with severe hypokinesia. Eye findings have not specifically been reported, but one would expect fixation disrupted by square-wave jerks, hypometria of horizontal and vertical saccades, normal saccadic velocity (except in advanced disease), impaired smooth pursuit, normal vestibular eye movements, impaired convergence, oculogyric crises, lid lag and reduced blink rate. Some patients in this group have coexisting antibodies to Ma1 and some of these patients with combined Ma1 and Ma2 antibodies have small cell lung cancer. Ma2 associated encephalitis has a better response to treatment than some other forms of paraneoplastic encephalitis, thus early diagnosis and recognition of the syndrome is important.

Another form of limbic encephalitis is that associated with the NMDA receptor antibodies, particularly seen in patients with ovarian teratoma. These patients present with a subacute psychiatric syndrome with amnesia, seizures, dyskinesias, autonomic instability, loss of consciousness and hypventilation.

Another form of encephalitis is seen in patients with voltage gated potassium channel antibodies (VGKC). These patients have autonomic dysfunction and neuromyotonia, REM sleep behavior abnormalities, and hyponatremia. This entity is an associated with thymoma and lung cancer.

CRMP-5 antibody is another antibody known to be a marker of encephalitis, peripheral mono-neuritis, dysautonomia, ataxia, myelopathy, optic neuritis and retinitis. It is most commonly associated with small cell lung cancer. In the 16 previously published case reports included in the article by Cross et al, 3 contained reports of nystagmus.

There are also patients reported in the literature with what clinically would be paraneoplastic encephalitis with serum antibodies which have not yet been identified. It is highly likely that there are many as yet unidentified antibodies which may be associated with patchy CNS inflammation. Any of these might be associated with inflammation in the brainstem, cerebellum and/or frontal and parietal lobes, and abnormal eye movements could be found. It is important to have a very high index of suspicion for a paraneoplastic disorder when seeing a patient with a new onset eye movement disorder.

Involvement of the brain stem can be seen in any of the above listed syndromes. Because this area may be affected with patchy inflammation, a wide variety of eye movement abnormalities can be seen including supranuclear palsy, intranuclear palsy, nuclear palsies, opsoconulus, and nystagmus of various kinds. These eye findings may be accompanied by other cranial nerve abnormalities and other brain stem abnormalities.

**Cerebellar degenerations** constitute a second major group of paraneoplastic disorders affecting eye movements. These generally present rather acutely with dizziness, nausea, vomiting, gait instability, oscillopsia, diplopia and then gait and appendicular ataxia, dysarthria and dysphagia. Early in the clinical course, the MRI of the head is usually normal, although sometimes the folia enhance. Cerebellar atrophy follows. The CSF shows inflammatory changes. The cerebellar syndrome may coexist with a more widespread encephalomyelitis. Small cell lung cancer is the most common associated malignancy and is present in 80%. Some patients also have a Lambert–Eaton syndrome with peak Q voltage gated calcium channel antibodies. It is not clear why the cerebellum is such a frequent target of paraneoplastic auto-immunity, but certainly the outcome is devastating for the patient. Downbeat nystagmus is the most common ocular motility finding. Waveforms often have increasing velocity, suggesting an unstable neural integrator. Other findings include horizontal gaze-evoked nystagmus, impaired smooth pursuit, saccadic intrusions and dysmetria.

There are nine marker antibodies which have been associated with cerebellar syndrome. These include:

1. Anti-Yo (also called Purkinje cell auto-antibody type 1 or PCA1) associated with breast cancer, tumors of the ovary, endometrium, fallopian tubes, where the target of the antigens are CDR proteins expressed by Purkinje and tumor cells.

2. Anti-TR directed against a cytoplasmic antigen of Purkinje cells and associated with Hodgkin’s lymphoma and these may be detectible in CSF and not in serum.

3. Anti-Hu (ANNA-1) sometimes with associated anti-PQ antibodies and this is associated with small cell lung cancer and very severe disability. These two antibodies can be present in patients with and without LEMS. In the patients with LEMS, treatment seems to improve the LEMS but not the cerebellar degeneration.

4. Anti-CV2 (also called CRMP–5) which is directed against a cytoplasmic antigen and glial cells and is associated with a wide variety of central and peripheral nervous system symptoms and signs, including severe cerebellar degeneration and optic neuritis. These patients may also have, for example, peripheral neuropathy and encephalomyelitis.

5. Anti-MA-1 directed against a protein in brain and testes and associated with testicular as well as breast, colon and parotid tumors.
6. Anti-ZIC-4 also is commonly associated with CRMP-5 antibodies and associated with small cell lung cancer.
7. Anti-mGluR1 found in two patients with Hodgkin’s lymphoma.
8. Anti-CARP VIII (carbonic anhydrase related protein) associated with melanoma.

It is clear that the range of antibodies that can be associated with degeneration of the cerebellum and cerebellar eye findings is very large. In these paraneoplastic entities, the 14–3–3 protein is sometimes found in CSF, but this appears to be a bystander and is secondary to brain degeneration, not to Jakob–Creutzfeldt disease. This can cause clinical difficulties because paraneoplastic encephalitis and Jakob–Creutzfeldt disease may look similar clinically.

Treatment in these cases is very difficult and the results depend on which antibodies are present. Prognosis is worse for anti-Yo and anti-Hu and slightly better for anti-TR and anti-CV2. IVIG, cyclophosphamide and methylprednisolone, and Rituximab have been used.

A third major category of paraneoplastic disorders causing eye movement abnormalities is opsoclonus myoclonus ataxia syndrome. This can be paraneoplastic, although it can also be due to effects from a virus, post-strep infection, metabolic abnormalities, metastases or intracranial hemorrhage. There are two main syndromes, a pediatric and an adult syndrome.

About 50% of children with opsoclonus myoclonus have neuroblastoma, while 2% of children with neuroblastoma develop opsoclonus myoclonus. Opsoclonus myoclonus precedes the diagnosis of neuroblastoma in half. Patients who have this paraneoplastic syndrome have a better overall prognosis than those neuroblastoma patients who do not. Auto–immunity is believed to underlie the syndrome, but the antigens have not been identified. It appears that there are multiple antibodies directed against a variety of CNS antigens. Reported therapies include steroids, ACTH, plasma exchange, IVIG, and chemotherapy. Sixty% of children have residual behavioral abnormalities.

The adult syndrome is associated with truncal ataxia and brain stem and cerebellar signs. The MRI is usually normal, but there can be T2 signal in the dorsal, pons and midbrain. Cancers associated with this syndrome include small cell lung cancer, breast cancer (especially if also ANNA–2 positive), gynecological malignancies, lung and bladder cancer.

The pathophysiology of these eye movements remains unclear. Leigh and Zee discuss the traditional attribution of the movements to abnormalities in the cerebellum, specifically the fastigial nucleus. A newer idea that this disorder is caused by malfunction of pontine and midbrain pause cells. Glycine is the neurotransmitter of the omnipause neurons, and patients poisoned with strychnine, a glycine antagonist, show opsoclonus and flutter. It is also possible that positive feedback loops and post–inhibitory rebound properties of premotor burst neurons are important in the generation of these eye movements.

Treatment has been attempted with clonazepam, thiamine and immunosuppressive drugs, as well as with immune-absorption with a protein A column. Anti–tumor treatment is also used. The prognosis is better with very prompt diagnosis and treatment. Unfortunately, the cerebellum can degenerate very quickly at which point the severe debilitating cerebellar findings are irreversible.

A fourth major category is that of the visual syndromes, including CAR, MAR and paraneoplastic optic neuropathy. These are being discussed by Dr. Keltner.

There is a group of syndromes affecting the spinal cord and dorsal root ganglia. These include motor neuron syndromes of subacute motor neuronopathy and ALS type syndromes which are atypical because the CSF protein is elevated. There is a lymphoproliferative picture in blood and there may be M–protein spike. These findings raise the suspicion that what presents as ALS might in fact be paraneoplastic. Other spinal cord and dorsal root syndromes include Stiff Person Syndrome and subacute sensory neuronopathy.

Amongst this group of paraneoplastic disorders, Stiff–Person Syndrome should be considered in patients with new eye movement abnormalities. The classical form of this disorder is characterized by progressive muscle stiffness, rigidity and spasm, particularly involving axial muscles. The spasms are triggered by various stimuli. EMG shows continued discharges of motor unit potentials. In addition to the classic motor abnormalities, these patients can have involvement of the brain with a cerebellar syndrome, an extrapyramidal syndrome, and an encephalitic picture. Diagnosis of a functional disorder is, unfortunately, quite frequent. There are three recognized subsets of this disorder:

1. An autoimmune variant associated with GAD–65 antibody, type 1 diabetes mellitus and other autoimmune disorders.
2. A paraneoplastic variant associated with the amphipysin antibody, seen particularly in patients with breast and small cell lung cancer.
3. An idiopathic variant without an identifiable antibody (35% of cases).

Eye movement abnormalities are quite varied. This depends on the specific parts of the nervous system affected. A confounding factor is whether there are eye movement abnormalities associated with any of the autoimmune disorders which may coexist with Stiff Person Syndrome (such as myasthenia gravis and thyroiditis). Nystagmus (including downbeat nystagmus with
concomitant ataxia), alternating skew deviation, (in the presence of ataxia), dysmetric saccades, oscillopsia, poor smooth pursuit, slow following movements, limited up and down gaze, and vertical and horizontal misalignment have all been reported. Oskarsson et al have reported a case of non-paraneoplastic Stiff–Person Syndrome with extrapyramidal features and anti CAD–65 antibodies in which they have recorded eye movements. The patient had a supranuclear vertical gaze palsy, vertical greater than horizontal hypometric saccades with prolonged saccade latency, saccadic vertical pursuit but normal horizontal pursuit and impaired convergence.

A further group of syndromes are those affecting peripheral nerve and muscle. In the peripheral nervous system, we can find subacute sensory neuropathy, chronic sensorimotor neuropathy associated with plasma cell dyscrasias, acute sensory motor neuropathy (Guillain–Barre), paraneoplastic autonomic neuropathy and paraneoplastic peripheral nerve vasculitis. A vasculitic syndrome can certainly involve cranial nerves III, IV and VI and can cause cranial nerve palsies.

Muscle syndromes/myoneural junction syndromes include myasthenia gravis with acetylcholine receptor antibodies associated with thymic hyperplasia and thymic epithelial tumors and also with small cell lung cancer, thyroid, breast cancer and Hodgkin lymphoma. There is also Lambert–Eaton myasthenic syndrome where antibodies are directed against voltage gated calcium channels. This presents with hip and then shoulder girdle weakness, muscle stiffness and myalgias, autonomic dysfunction, dry mouth and impotence. Oculobulbar symptoms can be present, but are relatively mild in contrast to true myasthenia gravis where they are sometimes much more severe. Fifty % of patients with Lambert–Eaton have cancer, usually small cell lung cancer.

Treatment of the muscle symptoms includes guanidine and pyridostigmine, IVIG and immunosuppression. Other muscle syndromes include dermatomyositis and polymyositis, paraneoplastic neuromyotonia, acute necrotizing myopathy and cacthetic myopathy.

It is, first of all, imperative to consider paraneoplastic disorders when seeing a patient with a new ocular motility disturbance. Since malignancy can present with paraneoplastic disease, no past history of tumor is required. Even disturbances which superficially fit a diagnosis of a degenerative disease or vascular disorder should have paraneoplasia considered. Although paraneoplastic processes are often characterized as “subacute”, i.e. in the category of inflammatory disease, sometimes symptomatically they are more “acute” (like vascular disease) or more “chronic” (like degenerative disease). When the picture is not classical for anything, this is the time to think of a paraneoplastic process.

The evaluation of patients with paraneoplastic syndrome is challenging. Routine blood work should be supplemented by an antibody panel. A standard panel of antibodies should be screened for, rather than a certain few. The reason for this is that a single syndrome can be associated with multiple different antibodies and a single antibody can be associated with more than one clinical syndrome.

Because antibodies may be absent in the serum but present in the CSF, the CSF should be subjected to the antibody panel screening as well. A lumbar puncture also allows for measurement of inflammatory markers, white cells, red cells, elevated protein, which can be very suggestive of a paraneoplastic process.

The MRI of the brain is sometimes useful. Early in the clinical course the MRI of the brain can be negative, but later there can be enhancement of involved areas, particularly in the encephalomyelitis and the cerebellar degeneration groups. In patients with opsooclonus, myoclonus, and glioblastoma, the tumor will be seen. In patients who have peripheral nervous system disease, nerve conduction and EMG are helpful. Nerve biopsy can be invaluable as well.

It is essential to do a very thorough search for a primary tumor, including CT scanning of the chest, abdomen and pelvis. In males, testicular ultrasound may be indicated. In women or men with or without palpable breast masses, mammography is essential. If these studies are negative, PET scanning may be of value. It can be sensitive in finding small areas of occult malignancy. Enlist the help of a colleague in internal medicine to help with detection of other immune processes and occult tumor.

The hunt for an occult primary can be extremely frustrating. In some cases, it is necessary to repeat this testing after a number of months have gone by. As mentioned above, in patients with testicular lesions, these can be so tiny as not to be findable in any way except for a pathological study of the testicles. Even more frustrating is the idea that in some patients these syndromes will exist and no primary tumor will ever be found.

Treatment is equally frustrating. There are two major ways of approaching treatment. The first is identification and treatment of the primary tumor. The second involves suppression of the immune response. In the group of peripheral nerve disorders, response to IVIG, plasmapheresis and immunosuppression is often reasonable. In disorders that are antibody mediated, namely the four or five disorders of neuromuscular junction and retina, B–cell treatment with Rituximab might be of benefit. For the other disorders, however, we are left with IVIG, plasmapheresis, immunosuppression, steroids and immunosuppression with drugs such as cyclophosphamide, tacrolimus and Cyclosporin. The earlier these disorders are discovered, the better the potential for prevention of worsening, however, many of them just are not treated satisfactorily in any way and particularly the cerebellum has degenerated, there is no going back.
**CME ANSWERS**

1. Encephalomyelitis, cerebellar degeneration, the syndrome of opsoclonus, myoclonus and ataxia, spinal cord and dorsal root ganglia (Stiff–Person Syndrome) and peripheral nerve and muscle (paraneoplastic Guillain Barre Syndrome)

2. Evaluations should include routine blood work and urinalysis, a full paraneoplastic antibody profile, CXR, CT of chest abdomen and pelvis, MRI of brain, lumbar puncture, PET scanning (if other tests are negative), testicular ultrasound (males) and mammogram (females, males with breast lesions).

3. Glucose, protein, cell count, flow cytometry and cytology, paraneoplastic antibody panel.

**REFERENCES**


