Paraneoplastic Syndromes in Neuro-Ophthalmology

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Abstract

Paraneoplastic neurological syndromes (PNS) occur in about 1 in 300 cases of cancer. The usual mechanism is that an antigen on the cancer sets off an immune response that then cross-reacts with a nervous system antigen. The presentation is usually with a subacute progressive neurological disorder. The management of these conditions is usually of both the underlying tumor and immunomodulation to suppress the autoimmune response. There are a number of these conditions that can present to the Neuro-Ophthalmology clinic, either as a discrete condition affecting vision or eye movements or as part of a more widespread neurological disorder. This article will discuss these conditions, their management and prognosis.

Keywords: Cancer, immunomodulation, neuro-ophthalmology, paraneoplastic autoantibodies, paraneoplastic neurological syndrome

INTRODUCTION

Paraneoplastic neurological syndromes (PNS) occur when there is a remote effect of a tumor within the nervous system due to some sort of immunological mechanism. They occur in about 1 in 300 cases of cancer. The usual mechanism is that an antigen on the cancer sets off an immune response that then cross-reacts with a nervous system antigen. These are often against intra-neuronal proteins whose pathological significance is not always clear but they act as a marker that there is a PNS present. These auto-antibodies are often, but not always, measurable in serum and can correspond to a specific neurological condition. The presentation is usually with a subacute progressive neurological disorder. When suspected, a screen for an underlying tumor needs to be carried out, which is found in about 65% of cases, sometimes some years after the initial presentation. The management of these conditions is usually of both the underlying tumor and immunomodulation to suppress the autoimmune response.[1]

There are a number of paraneoplastic syndromes that may affect afferent or efferent pathways involved in vision, either in isolation or as part of a more widespread neurological problem. This article will discuss some of the range of disorders that may present to the Neuro-Ophthalmology clinic.

Paraneoplastic optic neuropathy

Paraneoplastic optic neuropathies usually present with subacute painless vision loss that becomes bilateral within weeks or months. Other visual symptoms include blurred or dimmed vision, phosphenes, dazzling vision, tunnel vision and symptomatic visual field defects.[2‑3] The loss of vision may be severe. In one series, 10 out of 13 affected eyes had a presenting visual acuity ≤0.1 Snellen decimal.[3] In another series of 17 patients, the median visual acuity was 0.4 (range 1.0 to counting fingers).[4] Visual field defects reported include enlarged blind spots, arcuate and altitudinal defects, paracentral scotomas, peripheral constriction to cause tubular vision and general depression.[2‑3] Ocular and optical coherence tomography examination usually reveals swollen optic discs.[2‑4] This may be accompanied by nerve fiber layer hemorrhages, vitritis, iritis or retinitis.[2‑4] Fluorescein angiography may show optic disc hyper-fluorescence and leakage, sub-retinal fluid and peripheral retinal vessel leakage.[2] Electro-retinographic abnormalities reported include prolongation of the scotopic combined rod-cone (maximal) response, the photopic-cone response, and the photopic 30 Hz flicker response as well as a reduced and prolonged scotopic rod response.[2] Visual evoked potentials may show a delayed implicit period, low amplitudes or complete absence of a response.[1] Magnetic resonance imaging (MRI) may show prominence of the optic nerve sheaths on T2-weighted imaging and optic disc enhancement on post-gadolinium T1-weighted imaging.[3]

Pathological examination of the optic nerve in the condition has shown predominantly CD8 T cell infiltrates with expansion of fibrovascular septae and patchy loss of axons and myelin. Additional T cells infiltrates can be seen in the ciliary body muscle and around the central retinal artery and vein.[2] The characteristic antibody associated with paraneoplastic optic neuropathy is anti-CV2/collapsin response-mediator protein 5 (anti-CRMP5).[2‑4] although other reported associated...
antibodies include anti-amphiphysin, anti-paraneoplastic Ma antigen 2 (Ma2/Ta), anti-Yo and anti-Ma2.\(^7\)

Patients with paraneoplastic optic neuropathy and anti-CRMP5 antibodies may have a myriad of additional neurological symptoms including dementia, seizures, anosmia, ageusia, dysphagia, limb weakness, Parkinsonism, myoclonus, chorea, hemiballismus, dyskinesia, akathisia, ataxia, orthostatic intolerance, early satiety, constipation/diarrhea, dry mouth, nausea and weight loss.\(^2\)

The majority of patients with anti-CRMP5 antibodies have small cell lung carcinoma (SCLC). The other reported tumors include renal cell carcinoma and thyroid papillary carcinoma.\(^2\) Additional tumors reported in patients with paraneoplastic optic neuropathy without anti-CRMP5 antibodies are cervical carcinoma, testicular seminoma, thymoma, and colonic carcinoma [Figure 1].\(^3,5\)

A case series of 14 anti-CRMP5 positive patients with ocular involvement reported that 13 received immunomodulatory therapy including corticosteroids, cyclophosphamide, plasma exchange and intravenous immunoglobulin. The median final visual acuity was 0.5 (range 1.0 to hand movement perception). Visual acuity improved in 50% of treated patients. Out of the whole case series of anti-CRMP5 positive patients, 58% died within 5 years with a median follow-up from symptom onset of 9.5 months (range 1 to 128 months).\(^4\)

**Neuromyelitis optica spectrum disorder**

Neuromyelitis optica (NMO) spectrum disorder (NMOSD) may be a paraneoplastic disease. From a series of 41 NMOSD patients with positive NMO immunoglobulin G (IgG) antibodies, five had an identified underlying malignancy. These were breast carcinoma (two cases), breast carcinoma and leiomyosarcoma (one case), lymphoma (one case) and cervical carcinoma (one case). The mean age at onset was 48.8 years in this group compared with 36.7 years for the NMOSD patients without malignancy (p = 0.046). All of the patients had either unilateral or bilateral optic neuritis.\(^6\) Another study also found that patients with paraneoplastic NMOSD were also often older at symptom onset. The 17 paraneoplastic cases identified from their series and from a literature review had a median age of symptom onset of 55 years compared with 40 years in 151 non-paraneoplastic cases (p = 0.006). However, in this series only two of the 17 patients had optic neuritis. All of the cases were positive for anti-aquaporin 4 (AQP4) antibodies. The associated tumors were non-SCLC, breast carcinoma, oral squamous cell carcinoma, carcinoid tumors, papillary thyroid carcinoma, prostatic carcinoma, acute myeloid leukemia and mature B cell lymphoma.\(^7\)

Other paraneoplastic autoantibodies discovered in patients with NMOSD apart from anti-NMO IgG/AQP4 include type 1 antineuronal nuclear (ANNA-1) antibodies in one patient who also had anti-AQP4 antibodies\(^8\) and anti-CV2/CRMP5 in two patients who were negative for anti-AQP4 antibodies.\(^9,10\) A subsequent study suggested that there was no need to routinely screen NMOSD patients for other paraneoplastic antibodies if they already had a positive test for anti-AQP4 antibodies.\(^11\)

Reported outcomes from one case series of paraneoplastic NMOSD patients were that 10 out of 17 (59%) improved after immuodulatory treatment, although five (29%) died, compared with 8/151 deaths (5%) in the non-paraneoplastic NMOSD group.\(^7\)

**Papilledema**

Papilledema is usually a manifestation of raised intracranial pressure secondary to an intracranial tumor, cerebral venous sinus thrombosis (CVST) or pseudotumor cerebri (PTC). There are circumstances, however where it may have a paraneoplastic etiology. CVST may occur due to a systemic hypercoagulable state, which can either be due to hyperviscosity, that can occur with some malignancies, or can be paraneoplastic in origin. Cases of CVST have been reported in association with squamous cell metastatic cervical carcinoma, non-Hodgkin’s lymphoma, glomus tumors, colorectal carcinoma, epidermoid carcinoma of the tongue, dysgerminoma and Ewing’s sarcoma. The presence of malignancy should therefore be considered in any patient presenting with CVST.\(^12\)

PTC has been reported to occur in cases of chronic myeloid leukemia,\(^13\) acute myeloid leukemia,\(^14\) acute lymphoblastic leukemia\(^15\) and acute promyelocytic leukemia.\(^16\) In the leukemia cases successful treatment of the disease along with measures to reduce intracranial pressure, such as acetazolamide and cerebrospinal fluid (CSF) diversion surgery, have been reported to lead to resolution of the papilledema.\(^11,13-16\) Papilledema can also occur in POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes) syndrome. In this condition there is monoclonal plasma
cell proliferation leading to monoclonal immunoglobulin over-production (M-protein). In one study, papilledema was seen in 49 out of 94 (52%) patients with the condition. Over the course of the study 14 patients died. The median follow-up period for surviving patients was 5.6 years. The presence of papilledema at presentation was found to be an independent prognostic factor for death occurring (hazard ratio 1.58). [17]

**Myasthenia gravis**

Myasthenia gravis (MG) is an auto-immune disease typically due to antibodies to the acetylcholine receptor (AChR) at the post-synaptic neuromuscular junction. Additional antibodies have been discovered against muscle specific kinase (MuSK) and low-density lipoprotein receptor-related protein 4 (LRP4). MG causes weakness and fatigability of muscles. It typically affects ocular, bulbar and proximal limb muscles. In severe cases it can cause respiratory muscle weakness.[18] Between 10-15% of cases of MG are associated with the presence of a thymoma and 50% of thymoma cases have MG. The immune response against an epitope expressed on thymoma cells can cross-react with neuromuscular junction proteins, such as the AChR.[19] The vast majority of cases of MG associated with thymoma have anti-AChR antibodies, however cases of thymoma have been reported in cases with anti-MuSK antibodies and in seronegative MG,[19,20] therefore screening for thymoma should occur in all MG cases regardless of antibody status. Purely ocular MG has been reported to be associated with thymoma in 6.25% of cases from one case series.[21]

One study of 193 myasthenic patients as a whole with thymoma over a median follow-up period of 50.4 months, found that 50 (25.9%) patients achieved complete remission from their MG after resection of their thymomas and five (2.6%) died: one due to thymoma recurrence; three due to MG and one due to an unrelated cause.[22]

**Lambert-Eaton myasthenic syndrome**

Lambert-Eaton myasthenic syndrome (LEMS) is a disease caused by auto-antibodies to neuromuscular junction presynaptic voltage-gated calcium channels. It causes muscle weakness and autonomic dysfunction associated with depressed deep tendon reflexes that show post-tetanic potentiation. It is a paraneoplastic condition in about half of cases, with the vast majority of these cases due to SCLC. It does not cause as many ocular symptoms as MG and they are often mild and transient. In one series of 25 paraneoplastic LEMS cases, 11 (44%) reported double vision and 10 (40%) reported drooping eyelids. On examination, no ophthalmoplegia could be detected but 13 (52%) had ptosis and three (12%) had reduced pupillary reactions to light. [23] The ptosis may show transient improvement after sustained upgaze[24] and saccadic velocity may increase after carrying out saccadic exercises.[25] These phenomena are due the post-exercise facilitation of muscle contraction that is seen in LEMS, which is a distinguishing feature of LEMS from MG.[23-25]

Symptomatic treatment for LEMS is with drugs such as 4-aminopyridine or 3,4-diaminopyridine, which increase the release of acetylcholine from the presynaptic neuromuscular junction. Immunomodulation is usually required as well. Benefits have been reported from prednisolone, azathioprine, IVig and plasma exchange.[26] Additionally, treatment of the underlying tumor can lead to improvement and even remission of LEMS symptoms.[27] It has been reported that patients with SCLC associated with LEMS have a longer survival than patients with SCLC without LEMS (median survival 17 versus 7 months, P < 0.0001), even after correction for tumor stage. This may be due to an enhanced anti-tumor immunological response.[28]

**Nystagmus**

Paraneoplastic cerebellar degeneration (PCD) usually presents with acute or subacute gait ataxia. Characteristic auto-antibodies detected in these cases are anti-Yo, anti-Hu, anti-CV2/CRMP5, anti-Ri, anti-MA2 and anti-Tr. Typical tumors include SCLC, breast carcinoma, uterine carcinoma, ovarian carcinoma, thymoma and Hodgkin’s disease.[29] In a series of patients with PCD, nystagmus was present in 86% of cases with anti-Tr antibodies, 69% with anti-Hu antibodies, 68% with anti-Yo antibodies and 33% with anti-Ri antibodies.[30] Downbeat nystagmus, which can occur with increasing velocity waveforms, is the most common nystagmus pattern in PCD, although other patterns have been described including upbeat and horizontal gaze-evoked nystagmus.[31] In addition to nystagmus, ocular dysmetria, saccadic intrusions and oscillations, and skew deviation may also be seen in PCD.[32]

Despite the underlying cancer being treated and the use of various immunosuppressant agents, the prognosis in PCD is generally poor. The median survival times in one study was >113 months in anti-Tr cases, 7 months in anti-Hu cases, 13 months in anti-Yo cases and >69 months in anti-Ri cases. It is not clear why there is difference in survival time with the different antibodies, but anti-Tr cases still get significantly disabled from the disease.[29]

**Opsoclonus**

Opsoclonus is an eye movement disorder that is characterized by multi-directional conjugate saccades that occur without an inter-saccadic interval.[33] It frequently occurs with trunk and limb myoclonus, ataxia and dysarthria, when it is termed opsoclonus-myoclonus syndrome (OMS).[34] Both humoral and cell-mediated immune mechanisms have been implicated in its pathogenesis.[35] In a series of 114 adults, 45 (39%) had paraneoplastic OMS.[34] In a series of 389 children with OMS, 194 (50%) had a remote tumor detected.[35] The commonest associated antibodies in adults have been anti-Ri (ANNA-2) and glycine receptor antibodies. Other paraneoplastic antibodies that have been detected in adults include anti-Hu (ANNA-1), anti-Yo (PCA-1), anti-Ma1, anti-Ma2, anti-N-methyl-D-aspartate (NMDA) receptor, anti-ampiphysin, anti-CV2/CRMP5, anti-Zic2 and anti-neurofilaments.[33] These antibodies were not detected in children with paraneoplastic OMS.[35] The most frequent
associated cancers are neuroblastomas in children and breast cancer, SCLC and ovarian teratoma in adults.[33-35] Having paraneoplastic OMS has been reported to be associated with a higher chance of having relapsing disease compared with autoimmune OMS in adults (24% versus 7%).[34] In a pediatric series, tumor resection led to improvement of OMS in 42%, but no change or deterioration in 58%.[35]

Paraneoplastic brainstem encephalitis
Paraneoplastic brainstem encephalitis (PBE) can present with a variety of eye movement disorders including up- or downbeat nystagmus, horizontal or vertical gaze palsies, internuclear ophthalmoplegia, sixth nerve palsy and ptosis. There are usually other associated symptoms including vertigo, hearing loss, dysarthria and dysphagia. The commonly antibodies with PBE include anti-Hu, anti-CV2/CRMP5, anti-Ma2, anti-NMDA receptor and anti-kelch-like protein 11 (KLHL11). The most frequently associated cancers are SCLC (anti-Hu and anti-CV2/CRMP5), testicular germ cell tumors (anti-Ma2), ovarian teratomas (anti-NMDA receptor) and seminomas (anti-KLHL11).[1,32] In a series of 22 patients with anti-Hu associated brainstem encephalitis, 15 died within a median of 3 months from diagnosis, three of the six who survived had neurological improvement and one was lost to follow-up.[36] Out of 33 patients with anti-Ma2 associated encephalitis, 11 had objective neurological improvement after a median follow-up of 2.5 years, seven had stable disease after a median 3.5 years and 15 deteriorated over a median 9 months, including 12 who had died.[37] In a largely archive series of 13 patients in whom anti-KLHL1 antibodies were found on subsequent testing, nine had improvement or stabilization of their symptoms with treatment of the underlying tumor and immunosuppression over a median follow-up of 59 months.[38]

Pediatric paraneoplastic syndromes
The association of OMS with pediatric rhabdomyosarcoma has been discussed above. In addition, all the other PNSs discussed above have been reported to occur in childhood.[15,16,39-42] The antibody panels seem to be less sensitive and specific than in adult PNSs. The common tumor types diagnosed in pediatric PNSs are neuroblastoma, teratoma and lymphoma. The investigation and treatment is the same as for adults.[39]

DISCUSSION
When a PNS is suspected, the first step is to test serum for paraneoplastic autoantibodies. As has been discussed above, the clinical presentation will guide what antibodies to test for. In addition, particularly for the brain-involving PNSs, a lumbar puncture should be performed. This can help in ruling out other conditions, such as infection. In addition, an abnormal CSF with the presence of lymphocytes, raised protein or isolated oligoclonal bands in the absence of an infective etiology may give a clue that a PNS is present. However, a PNS may still be present with a completely normal CSF. Lastly, paraneoplastic autoantibodies may be detected in the CSF. The second step is to hunt for an underlying tumor. This will be guided by the clinical presentation but should include a thorough physical examination. Tumor markers, such as CA125 when an ovarian tumor is suspected, can also be measured. The choice of imaging study requested should again be guided by the presentation. An initial computed tomography (CT) scan of the chest, abdomen and pelvis, or 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scan, if available, should be performed if there are not clinical clues as to the tumor site. Testicular ultrasonography should be performed in men with anti-Ma2 antibodies, a pelvic ultrasound or MRI in women when an ovarian tumor is suspected and mammography in women when breast carcinoma is suspected.[1,43] If clinical suspicion of a PNS remains high, despite negative imaging results, imaging should be repeated 6 monthly for 4 years, since the causative tumor may remain radiologically invisible for some time.[43]

In general, as has been discussed, treatment of a PNS involves a combination of treating the underlying tumor and immunomodulation. The prognosis, in general, remains poor though.

In a study of 59 patients with PNS, 17 patients died with a median survival time from the onset of symptoms of 43 months.[44]

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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