

Acute neurological visual loss in young adults: causes, diagnosis and management

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ABSTRACT

Visual loss in the young adult can be caused by demyelinating diseases, inflammatory and autoimmune processes, infections, ischaemic events, and compressive lesions of the optic nerve. Diagnosis of the aetiologies of visual loss is reached by combining data from radiological studies, electrophysiological tests, and blood and cerebrospinal fluid analysis. Treatment is primarily aimed at decreasing the insult on the optic nerve and eventually controlling the primary disorder. The literature discusses separately the different aetiologies of visual loss. We present a review of the clinical characteristics of visual loss in the young adult, the different diagnostic measures, and the latest therapeutic strategies. The aim of this work is to summarise this entity in a practical way to guide clinicians in the diagnosis and management of this disorder.

INTRODUCTION

Acute visual loss is a medical emergency. An individual with acute unilateral visual loss is at a much higher risk of developing bilateral vision impairment and its devastating consequences.^{1–2} Patients who present with acute or subacute, unilateral or bilateral, visual loss attract the attention of both ophthalmologists and neurologists. Neurological disorders that may present with acute visual loss in patients between the second and fifth decade range from demyelinating diseases, infectious or inflammatory conditions, autoimmune disorders, compressive or infiltrative malignancies to hereditary diseases, and occasionally the aetiology is uncertain and the treatment is symptomatic with no defined diagnosis.¹ Neurological aetiologies for acute and subacute visual loss are varied and usually difficult to diagnose. Several investigations may be required to reach a definite diagnosis within the time and resource constraints. Furthermore, the visual outcome may depend on early management of the underlying pathology. We present a review of the clinical presentation of visual loss in the young adult followed by the different laboratory, radiological and electrophysiological studies necessary to differentiate and diagnose the aetiologies of visual loss in these patients (table 1). At the end of the article, we present an up-to-date review of the therapeutic measures available.

AETIOLOGIES

Demyelinating disorders

Epidemiology

The annual incidence of optic neuritis (ON) has been estimated at around 5–6.4 per 100 000 in the USA, with a prevalence of 115 per 100 000 and a female preponderance,^{3–4} and it increases at

locations of higher latitude compared with areas closer to the equator.⁴ Half of patients with ON eventually develop multiple sclerosis (MS).⁵

Clinical presentation

Acute inflammation of the optic nerve presents with monocular visual loss, usually acute, painful and progressive. This may be the first appearance of isolated ON or it may be the first presenting symptom of MS.³ If the visual loss is severe, it may be the first manifestation of neuromyelitis optica (NMO), which is less common than MS.⁵ Eventually, symptoms emanating from involvement of the cerebral white matter or the spinal cord establish the diagnosis. Optic neuropathy with symptoms and signs of upper motor neuron dysfunction suggests involvement of the cerebral white matter as in MS or acute disseminated encephalomyelitis (ADEM). Optic neuropathy with symptoms and signs of myelopathy such as a sensory level, sphincter dysfunction, sexual impotence, spastic paraplegia, and bilateral Babinski signs suggests NMO (table 1). Acute severe total loss of vision in one or both eyes is more suggestive of NMO than of MS.⁵

Laboratory investigations

Cerebrospinal fluid (CSF) studies are requested for most patients presenting with acute visual loss. The white blood cell count (WBC) in the CSF is marginally elevated in demyelinating diseases such as MS, with a mean of 12 cells/ μ L found in some cohorts of patients with MS.⁶ The CSF protein count can be slightly elevated in demyelinating diseases such as MS, with an average CSF total protein level in some MS cohorts of 0.27 g/L (range 0.16–0.71 mg/L),⁶ but high values above 1.0 g/L are mostly suggestive of infectious diseases. In demyelinating diseases, CSF IgG is usually elevated in comparison with that in the serum—increasing the IgG index—and protein electrophoresis reveals the presence of oligoclonal bands. Oligoclonal bands in the CSF are present in more than 90% of MS cases, but in only 15–35% of NMO cases.⁵ However, anti-aquaporin-4 antibodies is the test of choice to diagnose NMO. It is 76% sensitive and 94% specific for this disease when tested in serum, although it is usually elevated in CSF as well.⁵

Radiological investigations

MRI of the brain is the required test in patients with visual loss, as it may reveal pathology in the brain outside the optic nerve.⁷ The different MRI sequences should include axial and coronal imaging, as well as T1-weighted, T2-weighted,



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Table 1 Description of clinical symptoms, aetiologies and diagnostic studies of loss of vision in the young adult

Clinical presentation	Potential diagnoses	Targeted workup
Unilateral progressive loss of vision, periorbital pain on eye movement, upper motor neuron signs	Optic neuritis as part of multiple sclerosis	MRI of brain, orbits and cervical/dorsal spine with gadolinium, CSF IgG index and oligoclonal bands, VEP, BAER, SSEP
Severe optic neuropathy, myelopathy (sphincter dysfunction, impotence, bilateral Babinski signs, sensory level)	Optic neuritis as part of the neuromyelitis optica spectrum disorder	MRI of brain, orbits and cervical/dorsal spine with gadolinium, anti-aquaporin-4 antibodies in serum/CSF, VEP, BAER, SSEP
Optic neuropathy, cranial nerve involvement, systemic symptoms (fever, myalgias, arthralgias, weight loss, poor appetite)	Sarcoidosis, leptomenigeal disease (malignancy, infectious, syphilis, tuberculosis, cytomegalovirus, HIV, Epstein-Barr virus)	MRI of brain with gadolinium, CT chest/abdomen/pelvis with contrast, ACE in serum and CSF, CSF cytology, VDRL, HIV, PPD, TB, CMV and EBV-PCR, borrelia, brucella and bartonella serology, VEP
Optic neuropathy, dry ocular/oral mucosa, systemic symptoms (fever, arthralgias, myalgias, weight loss, poor appetite)	Sjogren syndrome	Anti-SSa, Anti-SSb, ANA, ESR
Optic neuropathy, oral and/or genital ulcers, skin lesions, uveitis	Neuro-Behcet's disease	HLA-B52, MRI of brain, orbits and cervical/dorsal spine with gadolinium
Optic neuropathy, malar rash, history of recurrent abortions, arthralgias, deep venous thrombosis	Systemic lupus erythematosus, antiphospholipid syndrome	Anti-dsDNA, lupus anticoagulant, anti- β 2-microglobulin, anti-cardiolipin antibodies
Progressive optic neuropathy, headache, tinnitus, vitiligo, poliosis	Vogt-Koyanagi-Harada syndrome	Melanin-laden macrophages in CSF
Slowly progressive unilateral loss of vision, optic disc atrophy	Extrinsic optic nerve compression (tumour, aneurysm or bone lesion), optic nerve sheath meningioma or glioma	MRI of brain and orbits with gadolinium, MRA, CT of brain, CT angiography, VEP
Subacute loss of vision, family history of loss of vision at a young age	Leber's hereditary optic neuropathy	Mitochondrial DNA point mutations (11 778, 14 484 and 3460)

ACE, angiotensin converting enzyme; ANA, antinuclear antibody; BAER, brainstem auditory evoked potentials; CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein barr virus; ESR, erythrocyte sedimentation rate; MRA; PCR, polymerase chain reaction; PPD; SSEP, somatosensory evoked potentials; TB, tuberculosis; VEP, visual evoked potentials; VDRL, venereal disease research laboratory.

fat-saturation T2, and pre- and post-gadolinium fat-saturated T1-weighted imaging.⁸ Patients with ON as a symptom of MS may have white matter lesions in the periventricular space or juxtacortical regions. The lesions are usually perpendicular to the ventricles and may well be increased in active disease. Lesions in the brainstem and cerebellar tracts also favour the diagnosis of MS in patients with ON. Sparse periventricular lesions and lesions in the periaqueductal grey suggest NMO in patients with ON⁵ (table 1). MRI of the spine is important to reveal involvement of other central nervous system sites as in MS or NMO. Spinal lesions in NMO are usually more extensive, covering at least three vertebral levels rather than the smaller lesions seen in MS⁵ (figure 1).

Electrophysiological investigations

Loss of visual acuity, with a normal eye examination, indicates significant optic fibre damage without localising the lesion. Severe loss of visual acuity is seen more in NMO than in ON associated with MS. Visual evoked potential (VEP) studies confirm involvement of the optic nerve and optic tracts. A delay in the P-100 latency with preserved N-P amplitude and wave morphology suggests a demyelinating pathology as in MS and NMO, while a decrease in N-P amplitude and deterioration in the wave morphology with a slight delay in the P-100 latency suggests axonal damage rather than focal demyelination, as in compressive or infiltrative diseases, such as tumours, internal carotid aneurysms or sarcoidosis.⁹

Electrophysiological studies should be completed with brainstem auditory evoked responses (BAER) and somatosensory evoked potentials (SSEP) to evaluate the extent of the disease, as it may involve subclinically other white matter tracts. Abnormal VEP associated with abnormal BAER and SSEP suggests a diffuse demyelinating disease such as MS rather than focal optic nerve pathology.

Optical coherence tomography of the optic nerve head reveals swelling of the peripapillary retinal nerve fibre layer (pRNFL) in acute ON. On the other hand, thinning of the pRNFL and the macular ganglion cell/inner plexiform layer



Figure 1 MRI of the cervical spine (T2-weighted image, sagittal view) revealing a longitudinal intraspinal lesion extending from vertebral levels C2 to C7.

reflect retrograde neurodegeneration due to axonal damage in cases of chronic optic neuropathy.

Infectious and inflammatory disorders

Clinical presentation

ON presenting with other systemic features such as fever, myalgia, arthralgia, loss of weight, decreased appetite and other symptoms suggests a systemic illness presenting with optic nerve involvement as its first manifestation. These systemic diseases include sarcoidosis,^{10 11} tuberculosis,¹² Vogt–Koyanagi–Harada (VKH) syndrome,¹³ rheumatological disorders such as systemic lupus erythematosus,¹⁴ Sjogren syndrome,¹⁵ and neuro-Behcet,¹⁶ as well as systemic viral infections such as cytomegalovirus (CMV),^{17 18} HIV¹⁹ and Epstein–Barr virus (EBV).^{20–23} One or both eyes may be involved. Changes of papillitis are seen on assessment of the optic nerve head (figure 2).

The presence of hilar lymphadenopathy usually points to the diagnosis of sarcoidosis. Recurrent oral and genital ulcers suggest the diagnosis of Behcet's disease. A history of tinnitus, headaches, poliosis and vitiligo suggests VKH syndrome. Ophthalmologists and infectious disease specialists diagnose infections of the retina such as tuberculosis, toxocara, bartonella and borellia.

Optic neuropathy can present with involvement of other cranial nerves—for example, loss of hearing, peripheral facial palsy, dysphagia, dysarthria, tongue deviation and ophthalmoplegia. Diseases causing these scenarios can be inflammatory (such as sarcoidosis), infectious (such as tuberculosis), infiltrative (as in malignancies, lymphomas, meningeal carcinomatosis) or compressive secondary to meningeal hypertrophy (as in Rosai–Dorfman disease² or extramedullary haemopoiesis due to thalassaemia).^{24 25}

Investigations

Anaemia and elevated erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) can be seen in infectious or inflammatory conditions presenting with visual disturbances. Elevated ACE levels in blood and CSF are seen in around 60% of patients with sarcoidosis.²⁶ Anti-cardiolipin antibodies are seen in anti-phospholipid syndrome. Antinuclear antibodies and elevated anti-SSa and anti-SSb antibodies suggest a rheumatological condition, specifically Sjogren syndrome. Anti-double-stranded DNA and lupus anticoagulant are seen in systemic lupus, which can eventually present with visual loss.¹⁴ In uncertain aetiologies, more extensive testing is sometimes requested and may include studies for EBV, CMV, borrelia, bartonella, brucella, tuberculosis, syphilis, folate and vitamin B12 (table 1). Abnormal CSF results with elevated WBC and low glucose

levels are seen in bacterial, cryptococcal and tuberculous meningitis. Oligoclonal bands can occasionally be seen in infectious or inflammatory diseases of the central nervous system (CNS).²⁷ Malignant cells are seen in leptomeningeal metastases.²⁷ Melanin-laden macrophages are typical of VKH syndrome.¹³ Oligoclonal bands can occasionally be seen in infectious or inflammatory diseases of the CNS.²⁷

Radiological investigations

Inflammatory lesions of the optic nerves usually extend along the borders of the nerve itself, sometimes causing thickening of the nerve, and are usually enhanced with gadolinium and best seen with T1-weighted fat saturation imaging.²⁸ MRI lesions limited to the meninges, sparing the cerebral parenchyma, suggest meningeal disease as the aetiology of the loss of vision as in meningeal carcinomatosis, infiltrative lymphoma, or sarcoidosis. MRI findings may not be enough for the definite diagnosis of these entities, and laboratory studies or meningeal biopsy may be necessary. CT of the chest and abdomen is sometimes required to confirm systemic disease in patients with loss of vision. Hilar lymphadenopathy suggests sarcoidosis or tuberculosis. Lymph node enlargement suggests systemic disease or malignancy.

Compressive lesions

Clinical presentation

Compression of the optic nerve as it exits the globe or optic foramen can cause acute or subacute progressive monocular visual loss. Tumours are usually of benign type such as dural meningiomas or optic nerve sheath meningiomas and rarely optic nerve gliomas^{29 30} (figure 3). Other tumours include craniopharyngiomas and pituitary adenomas. Compression of the optic nerve by a growing internal carotid aneurysm can cause visual loss and proptosis^{31 32} (figure 3). Other less common benign masses have been reported to present with loss of vision due to compression of the optic nerve, such as myofibromas of the orbit, osteopetrosis, pyknodysostosis, Rathke's cleft cyst, clinoid mucocele, fibrous dysplasia of the skull, and sphenoid sinus plasmacytoma.^{33–37} Slow progressive loss of vision restricted to one eye may suggest a slow growing optic nerve tumour. These tumours do not usually cause increased intracranial pressure and thus the optic nerve examination is normal or shows atrophy mimicking retrobulbar neuritis rather than papilloedema.

Investigations

CSF cytology to search for malignant cells is also requested in cases with multiple cranial nerve involvement or associated

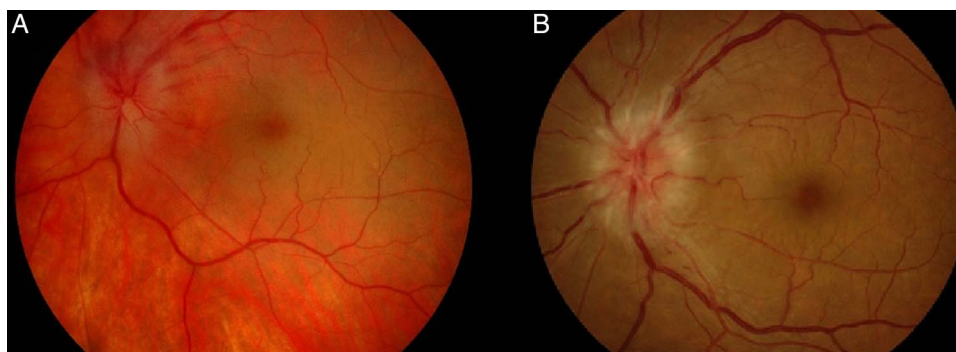


Figure 2 (A) Fundus image of acute ischaemic optic neuropathy. (B) Fundus image of sarcoidosis with the classical cherry red spot appearance.

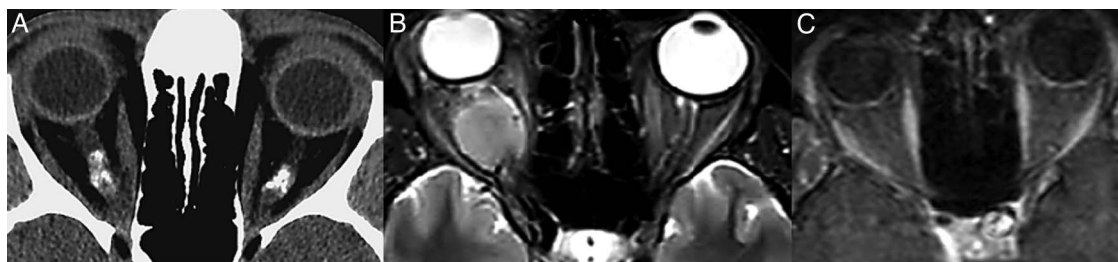


Figure 3 (A) CT of the orbits (axial view) revealing calcification of the optic nerves in optic nerve sheath meningiomas. (B) MRI of the orbits (axial view) revealing a right optic nerve glioma. (C) MRI of the orbits (axial view) revealing an internal carotid artery aneurysm compressing the left optic nerve at its exit from the optic canal.

cerebral lesions because of its specificity for malignancy. The presence of malignant cells in the CSF depends on the amount of CSF examined, time from CSF collection to histological examination, and the type of malignancy itself (intraparenchymal vs leptomeningeal involvement) (table 1). In cases with pathologies amenable to biopsy, a stereotactic or open biopsy should be performed if a diagnosis cannot be reached by non-invasive means. The advantage of an open biopsy is that it may include meningeal as well as parenchymal tissue.

Radiological investigations

Tumours of the optic nerve can be readily identified on MRI of the orbit. Meningiomas are extrinsic to the nerve and usually enhance.³⁸ Gliomas may be intrinsic and may or may not enhance (figure 3), but usually present with thickening with coronal imaging and high T2 signal between the globe and the optic chiasm. Optic nerve sheath meningiomas arise from the nerve sheath, are usually thin, and may extend with the dura to the splenium cavernosum and sometimes to the chiasm, contralateral optic nerve, or intracranially. Confirmation of the pathology can be achieved by unenhanced CT imaging of the orbit, which may reveal calcifications³⁸ (figure 3), and enhanced MRI imaging. Spine MRI is also important in diagnosing CNS tumours such as lymphomas.

Other causes

Rare neurological causes of visual loss in the young adult include Leber's hereditary optic neuropathy. This is suspected from a positive family history of loss of vision in the young and diagnosed by genetic testing, since the majority of such patients have one of three mitochondrial DNA point mutations (11 778, 14 484 and 3460).³⁹ Rosai-Dorfman disease is an infiltrative disease of histiocytes and lymphocytes that causes progressive loss of vision by impingement of hypertrophic dura on the optic nerve.² There are cryptogenic causes of loss of vision in the young adult where the presenting symptom is visual loss with no defined aetiology. Treatment is symptomatic to save vision until a diagnosis is established.

Investigations

Blood analysis for mitochondrial DNA point mutations (11 778, 14 484 and 3460) is specific for Leber's hereditary optic neuropathy.³⁹

TREATMENT STRATEGIES

Emergency treatments

Visual loss in the young adult is always considered a medical emergency and treatment should be initiated as soon as possible to preserve vision and avoid further axonal loss. Serum and CSF studies should be requested before treatment in order to identify

the causative agent or immunological response, which may be lost early in the course of treatment. The first treatment for acute or subacute visual loss in the young adult should be high-dose methylprednisolone pulse treatment at a dose of 1000 mg intravenously as an infusion for 3–5 consecutive days.⁴⁰ If vision improves and a relapse occurs in the weeks or months thereafter, another pulse dose can be administered. Pulse steroids provide symptomatic relief and are administered even though many studies have shown that steroids do not significantly decrease the degree of vision loss after the acute phase of ON.⁴⁰

Disease-specific treatment

If the aetiology for the visual loss has been established to be MS, then follow-up treatment with disease-modifying agents, such as interferons (interferon β -1a, 30 μ g intramuscularly once a week or 44 μ g subcutaneously three times a week; interferon β -1b, 0.25 mg subcutaneously every other day), glatiramer acetate (20 mg subcutaneously once a day or 40 mg subcutaneously three times a week), fingolimod (0.5 mg orally daily) or natalizumab (300 mg intravenous infusion over 1 h every 4 weeks) should be administered, with the choice of treatment depending on the clinical settings. If NMO is the diagnosis, then rituximab is the drug of choice (375 mg/m² body surface area intravenous infusion weekly over 4 weeks every 6 months, or two doses of 1000 mg intravenous infusion 2 weeks apart every 6 months).⁴¹

In inflammatory conditions such as sarcoidosis or connective tissue disorders, the treatment is initially pulse steroid therapy followed by long-term immunotherapy with either azathioprine (initially 1 mg/kg/day orally, increased according to response by 0.5 mg/kg/day after 4–8 weeks, not to exceed 2.5 mg/kg/day), methotrexate (7.5 mg orally as a single weekly dose, or 2.5 mg orally every 12 h for three sequential doses per week, to be increased according to response, not to exceed 20 mg/week) along with 5 mg folic acid orally once a week, preferably the day after methotrexate, or mycophenolate mofetil (dose range 0.5–3 g/day orally, depending on response).

Ischaemic optic neuropathies are usually managed by antiplatelet therapy and control of risk factors such as hypertension, diabetes and smoking. Visual loss secondary to optic nerve head infection should be treated with the appropriate antibiotic, antiviral or anti-parasitic therapies by the ophthalmologist. Compressive lesions such as meningiomas or gliomas are usually treated by surgical decompression. The decision about surgery depends primarily on the degree and progression of visual loss and the type and localisation of the tumour.⁴² Progressive visual loss, malignant tumours and extension into the cerebral hemisphere favour surgical intervention. Infiltrative malignancies such as metastatic meningeal carcinomatosis or lymphomatosis

are treated by systemic and intrathecal and intraocular chemotherapy. Stereotactic and whole brain radiotherapy are also treatment strategies for infiltrative disease. Internal carotid aneurysms compressing the optic nerve are investigated by cerebral angiography. Aneurysms amenable to endovascular intervention can be treated by these procedures to avoid the morbidity and mortality of craniotomy.⁴³

Plasmapheresis and intravenous immunoglobulin (IVIG; 0.4 g/kg/day intravenous infusion daily for 5 days then 400 mg/kg single dose monthly) are the treatments of choice in severely progressive visual loss that is not arrested by intravenous steroid pulse therapy, especially when the aetiology is considered to be autoimmune or inflammatory. In contrast, IVIG treatment for acute visual loss is not a well-established treatment.⁴⁰ It is used primarily in cases that fail or relapse after the conventional treatment. IVIG has been reported to be successful in stopping progression of visual loss or in improving vision in anecdotal cases.^{44 45} The choice between the use of plasmapheresis or

Main messages

- ▶ Visual loss in the young adult is a medical emergency.
- ▶ Neurological causes of visual loss in the young adult should be sought after ophthalmological causes have been ruled out.
- ▶ Aetiologies of visual loss in the young can be defined by a proper history and physical examination, in addition to laboratory testing, radiographic imaging and electrophysiological evaluation.

Current research questions

- ▶ Is it possible to find potent immunotherapy that can control the immune system without suppressing the bone marrow?
- ▶ Is it possible to culture stem cells to replace dying retinal neurons?
- ▶ Is it possible to produce a drug to protect the optic nerves from infiltrating diseases or cancers?

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Self assessment questions

Which of the following are true:

1. Optic neuritis usually presents with
 - A. Acute visual loss
 - B. Monocular visual loss
 - C. Painful visual loss
 - D. All of the above
2. The spinal cord lesions of neuromyelitis optica usually differ from those seen in multiple sclerosis in the following:
 - A. Extension over several vertebral bodies
 - B. Multiple in number
 - C. Enhancing lesions
 - D. Usually in the cervical cord
3. Serum ACE is:
 - A. Usually elevated in patients with sarcoidosis affecting the optic nerve
 - B. Not always elevated in patients with sarcoidosis
 - C. Elevated in patients with sarcoidosis and demyelinating CNS lesions
 - D. None of the above
4. Oligoclonal bands:
 - A. Are only seen in patients with multiple sclerosis
 - B. Are always seen in patients with multiple sclerosis
 - C. Are seen in multiple CNS lesions, but not in isolated optic nerve lesions
 - D. Can also be seen in infections or vasculitic diseases of the CNS
5. Treatment with high-dose intravenous steroid therapy:
 - A. Should be administered in acute optic neuritis
 - B. Should be administered in acute transverse myelitis
 - C. Should be avoided in undiagnosed CNS lesions
 - D. All of the above

IVIG depends primarily on the general condition of the patient, availability and cost. Patients with unstable cardiovascular condition or history of hypercoagulable state may not be good candidates for plasmapheresis, while patients with renal failure or IgA deficiency should not receive IVIG treatment.

It is important to consider that some autoantibodies can be suppressed or washed out after plasmapheresis or IVIG therapy. Inflammatory markers in the serum and CSF can be altered with all forms of treatment, especially intravenous corticosteroid therapy. Even changes on MRI, especially enhancement characteristics, as well as evoked potential abnormalities can decrease after immunotherapy.²⁷

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Answers

1. D
2. A
3. B
4. D
5. D