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Original Article

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A 16-Year-Old Girl With Bilateral Visual Loss and Left Hemiparesis Following an Immunization Against Human Papilloma Virus

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We report the course of a 16-year-old girl who presented with near complete visual loss associated with chiasmal neuritis and a biopsy proven tumefactive demyelinating lesion on magnetic resonance imaging (MRI) in association with a recent immunization against human papilloma virus.

Keywords: demyelination; tumefactive; blindness; chiasm; HPV

Visual loss is a symptom that can occur from lesions anywhere along the visual pathways. Binocular visual loss can be further localized depending on the size and location of the scotoma identified on examination. Lesions affecting the chiasm, in particular, may produce bitemporal visual field loss and the additional involvement of the optic nerves and/or retrochiasmatic visual pathways will induce more complete degrees of blindness. There are a multitude of etiologies that produce this latter pattern of visual loss; however, the pace of progression, the anatomic localization of the process, and the precipitating circumstances will aid in pathophysiologic classification as compressive or noncompressive. Noncompressive etiologies involving the chiasm include processes within the spectrum from acute to a more chronic temporal course. This slower time course is characteristic of infiltrative lesions, granulomatous diseases, axonal dieback phenomenon secondary to multiple sclerosis,[1] and Leber hereditary optic neuropathy. Acute noncompressive lesions of the optic chiasm have been described in infectious settings with Lyme disease,[2] Epstein-Barr virus,[3,4] varicella zoster virus[5] and mumps,[6] systemic lupus erythematosus,[7,8] and demyelinating processes (eg, neuromyelitis optica and multiple sclerosis). Tumefactive demyelinating lesions are those defined as large (>2 cm) lesions with a surrounding zone of edema with or without accompanying mass effect. There have been a few case reports and case series in the literature where tumefactive lesions have been described in the context of both multiple sclerosis and acute demyelinating encephalomyelitis. However, chiasmal neuritis as part of acute demyelinating encephalomyelitis has not to our knowledge been reported in the medical literature. Although chiasmal neuritis generally tends to have a more favorable outcome with eventual return of vision over time, when it is caused by neuromyelitis optica and Leber hereditary optic neuropathy the outcomes have been poorer with sustained visual loss. We report the case of a 16-year-old girl who suffered an acute and sustained onset of bilateral visual loss and transient left hemiparesis following an immunization against human papilloma virus, who was found to have both a tumefactive demyelinating lesion and chiasmal neuritis as part of a presentation of acute demyelinating encephalomyelitis.

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Case Report

A 16-year-old previously healthy girl presented to the emergency room with an acute onset of visual loss over 48 hours. Initially, there was visual loss noted in the right eye accompanied by a left side headache. These symptoms

worsened over the next 24 hours to include visual loss involving the left eye with a more diffuse headache. When evaluated in the emergency room at 48 hours after onset, her vital signs were blood pressure 116/65, pulse 68/minute, respirations 14/minute, and temperature 98°C,[6] with a completely normal general physical examination and no signs of systemic illness. Her examination disclosed a visual acuity of only counting fingers bilaterally with mild left side weakness accompanied by sensory loss to pinprick in the left arm. There was a left afferent pupillary defect and normal fundoscopic examination. Her visual ability deteriorated further to inconsistently identifying light and movement from the left eye only. She complained of no other symptoms and denied antecedent trauma or prodromal illness. She had, however, received her second vaccination against human papilloma virus 10 days prior to her presentation. There was no family history of demyelinating disease, collagen-vascular disease, or rheumatological disorders.

Magnetic resonance imaging (MRI) of the brain showed swollen enhancement within the chiasm extending into both retrobulbar optic nerves and a right occipitoparietal lobe mass (later disclosed as tumefactive demyelination) with a large zone of surrounding vasogenic edema (Figure 1). Complete spine MRI was normal. Biopsy of the hemispheric mass was performed and histology revealed demyelination (Figures 2 and 3). Subsequent cultures for aerobic and anaerobic bacteria, fungus, acid fast bacilli, and examination for parasites were negative as were serum immunoglobulin G and immunoglobulin M titers for *Toxoplasma gondii*. The erythrocyte sedimentation rate was 16 and the white blood cell count was 6900 with 89% granulocytes and 9% lymphocytes. The patient received a 5-day course of high-dose intravenous steroids (1 g methylprednisolone/d divided each 6 hours), followed by 5 double-volume plasma exchanges with no visual improvement. Other diagnostic testing included neuromyelitis optica (neuromyelitis optica-immunoglobulin G), antinuclear antigen, Sjögren syndrome (SS-A, SS-B), rheumatoid factor, angiotensin-converting enzyme, which were all normal or negative. Cerebrospinal fluid analysis was declined by the patient's family at this time. The family refused further therapy with chemotherapy and modulating agents. Three months after the onset, the patient still had not regained any visual function, her weakness and sensory deficit recovered completely however. A repeat MRI of the brain revealed resolution of the hemispheric and chiasmal lesions (Figure 4). At 6 months her funduscopic examination disclosed bilateral optic disc pallor. A repeat MRI at this time demonstrated no new lesions and continued resolution of the previously identified chiasmal enhancement and tumefactive lesion. Again complete spine MRI was normal. Cerebrospinal fluid was obtained 6 months after initial symptom onset. Cerebrospinal fluid cytology was negative for malignancy; additional studies revealed a clear and colorless fluid with 3 white blood cells and 0 red blood cells per microliter, glucose 61 mg/dL and simultaneous serum glucose of 91 mg/dL, protein 30 mg/dL, lactate 1.5 mmol/L, and negative oligoclonal immunoglobulin G bands. At 18 months after the onset of her symptoms, her examination remained stable with no further neurological complaints, persistent profound visual impairment, inconsistently identifying light and movement from the left eye only. An MRI of the brain was performed and was unchanged compared with the previous one done at 6 months (Figure 5).

Discussion

After a first demyelinating event, the 3 main diagnostic considerations are multiple sclerosis, acute demyelinating encephalomyelitis, and neuromyelitis optica. The clinical symptoms and signs, radiological findings, laboratory results, and clinical course help determine the likely diagnosis, with time often being the most crucial component.

On clinical grounds, our patient had bifocal chiasm and right parieto-occipital lesions occurring 10 days after a human papilloma virus vaccination, with a rapid progression over 2 days. There were no further demyelinating events within the next 18 months. In the context of prior vaccination in a 16-year-old girl, acute demyelinating encephalomyelitis is likely to explain the multifocal deficits. This demyelinating event could also represent the index attack of neuromyelitis optica known to cause severe bilateral visual loss due to optic neuritis with poor recovery. Her neuromyelitis optica-immunoglobulin G antibody was negative. However, this test has a sensitivity of approximately 70%. Permanent visual loss is not specific to neuromyelitis optica. Prior studies of optic neuritis from all etiologies encountered in childhood have shown good recovery is usual and that poor visual recovery occurred in less then 20% of children.[9,10] The monophasic course of our patient's demyelinating event and the lack of "dissemination in time," make a diagnosis of clinically definite multiple sclerosis unlikely. At this time, a divergence of opinion is notable from authors of various case series attempting to identify predictive factors of clinically definite multiple sclerosis in children who present with a first central nervous system demyelinating event or initial bilateral optic neuritis.[11,12]

In this instance, there was no supportive clinical or laboratory evidence for systemic lupus erythematosus, Sjögren syndrome, or Lyme infection. Other viral studies were unrevealing or negative. Bilateral visual loss due to involvement of the optic chiasm, as revealed on MRI in our patient, is a rarely described feature of demyelinating entities. The few reported cases of acute chiasmal neuritis in the post-MRI era have occurred in the context of infections with Lyme disease,[2] varicella zoster virus,[5] postinfectious Epstein-Barr virus[3,4]and mumps,[6] systemic lupus erythematosus,[7,8] neuromyelitis optica,[13,14] and

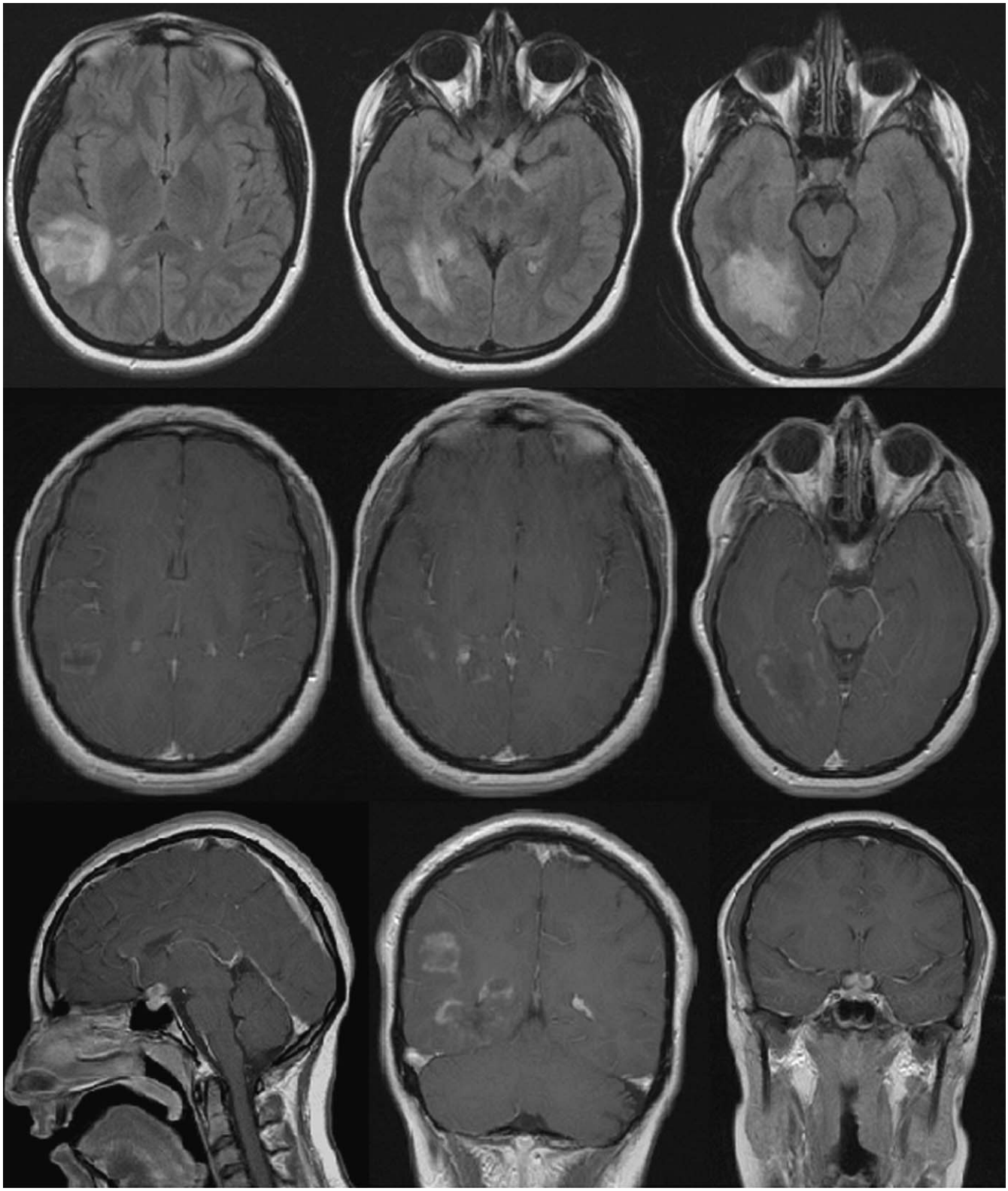

Figure 1. Magnetic resonance imaging on admission. Top: Fluid-attenuated inversion recovery sequences show right occipito-parietal and chiasmal increased signal. Middle: Axial T1 with contrast shows ring enhancement of the right occipito-parietal lesion. Bottom: T1 with contrast; on the left a sagittal view shows chiasmal enhancement, on the center and right coronal views show right hemispheric and chiasmal enhancement respectively.

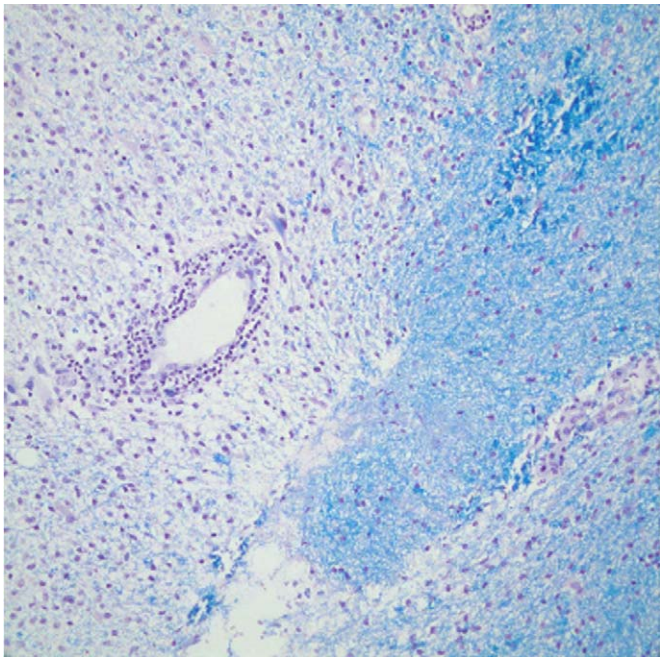

Figure 2. Photomicrograph at low power demonstrating demyelination on left half of field with a vessel cuffed with lymphocytes. Right-hand side of the field shows white matter with intact myelin (stained blue) but infiltrated with macrophages. Stained with Holmes Luxol fast blue, ×200 magnification.

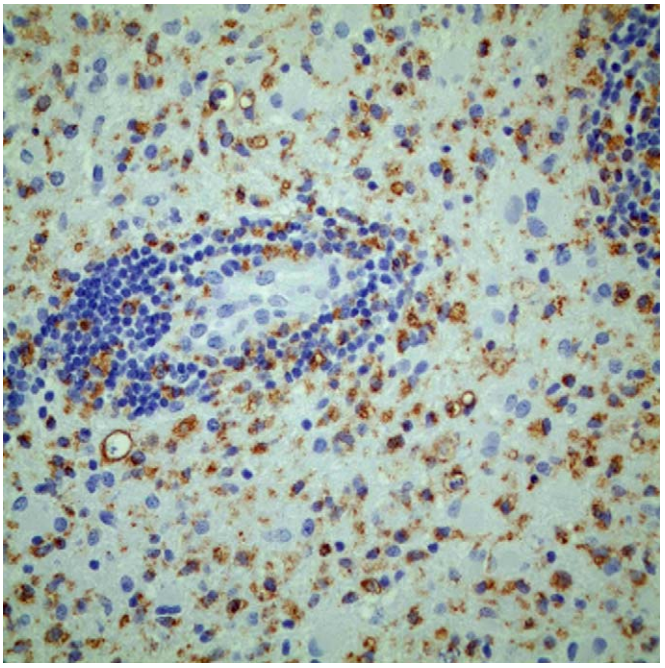

Figure 3. Photomicrograph at high power demonstrating a vessel cuffed with lymphocytes within a field of demyelination and infiltrated with macrophages. Stained with immunoperoxidase PGM1 for macrophages (brown), ×400 magnification.

multiple sclerosis[15] (see Table 1). Except in cases caused by neuromyelitis optica and varicella zoster virus, the clinical outcomes generally evolved toward improvement of visual function. It is difficult to assess in retrospect and therefore not known whether some of the children previously reported with bilateral optic neuritis also had involvement of the optic chiasm because it was not specifically delineated as such in prior reports.

Our patient was also unique in regard to the large tumefactive plaque identified. Tumefactive lesions can be identified in both multiple sclerosis and acute demyelinating encephalomyelitis and thus, are not specific for either. The international pediatric MS group described tumefactive lesions as one of the 4 patterns commonly encountered in acute demyelinating encephalomyelitis.[9] These lesions were also found by Ebner et al[16] to herald multiple sclerosis when it starts in childhood. In a recent article, large demyelinating lesions were significantly more often associated with monophasic central nervous system demyelinating events when compared with multiple sclerosis but were not exclusive to acute demyelinating encephalomyelitis.[12] In a recent review of the literature on tumefactive demyelinating lesions in childhood carried out by Dastgir and DiMario,[17] 50% of these children had subsequent clinical relapse or developed multiple sclerosis.

Neuromyelitis optica remained a diagnostic consideration in the patient presented here in spite of the occipito-parietal lesion. An abnormal brain MRI does not exclude a diagnosis of neuromyelitis optica according to the recently revised diagnostic criteria.[18] Furthermore, most patients with neuromyelitis optica complicated by the concurrent development of large brain lesions on MRI were children.[14,19]

The radiological resolution of the chiasmal lesion preceded the occipito-parietal lesion by months. Although the patient's left arm weakness improved to complete recovery promptly on steroid therapy, the visual loss persisted. This dissociation of the clinico-radiographic evolution may suggest a clinical feature in favor of acute demyelinating encephalomyelitis over the progressive lesions of multiple sclerosis and neuromyelitis optica.

Tumefactive demyelinating lesions are not infrequently explored surgically because there are no specific radiologic features that distinguish this acute inflammatory demyelinating process from a neoplastic one. The histopathology allows this differentiation in the acute setting but differentiating between different acquired demyelinating entities (ie, acute demyelinating encephalomyelitis, multiple sclerosis, and neuromyelitis optica) has proven to be a much more complex task. The addition of specific serum antibody tests and the clinical course over time are needed at this juncture to secure diagnosis.

Various vaccines have been associated with acute demyelinating encephalomyelitis, but except for the Semple vaccine,[20] a definite causal effect cannot be

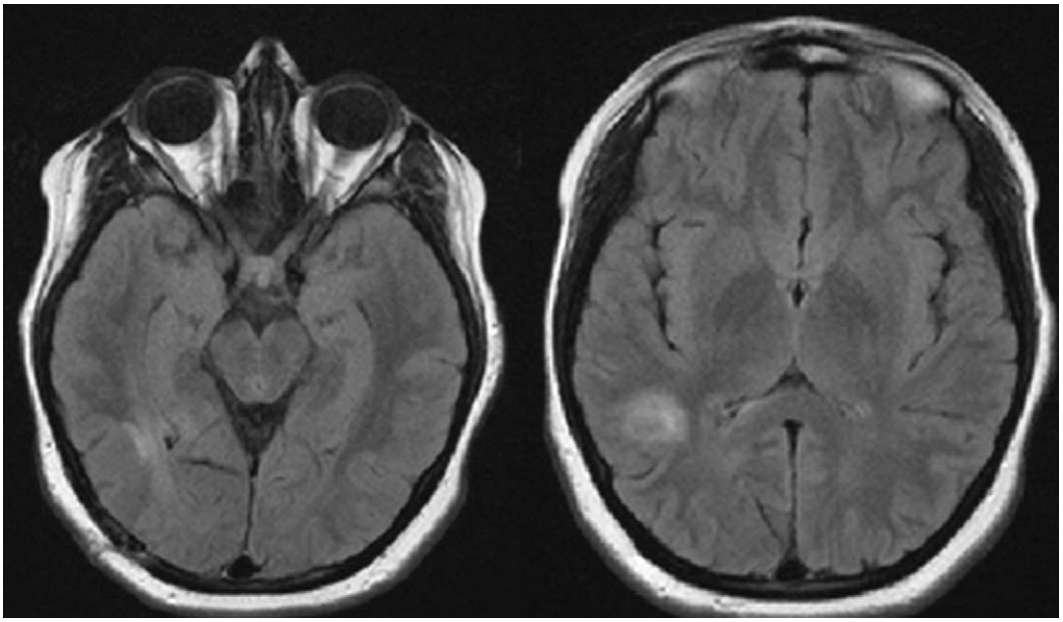

Figure 4. Magnetic resonance imaging 3 months after initial admission. Fluid-attenuated inversion recovery sequence with lessening of the high signal intensity compared with admission scans.

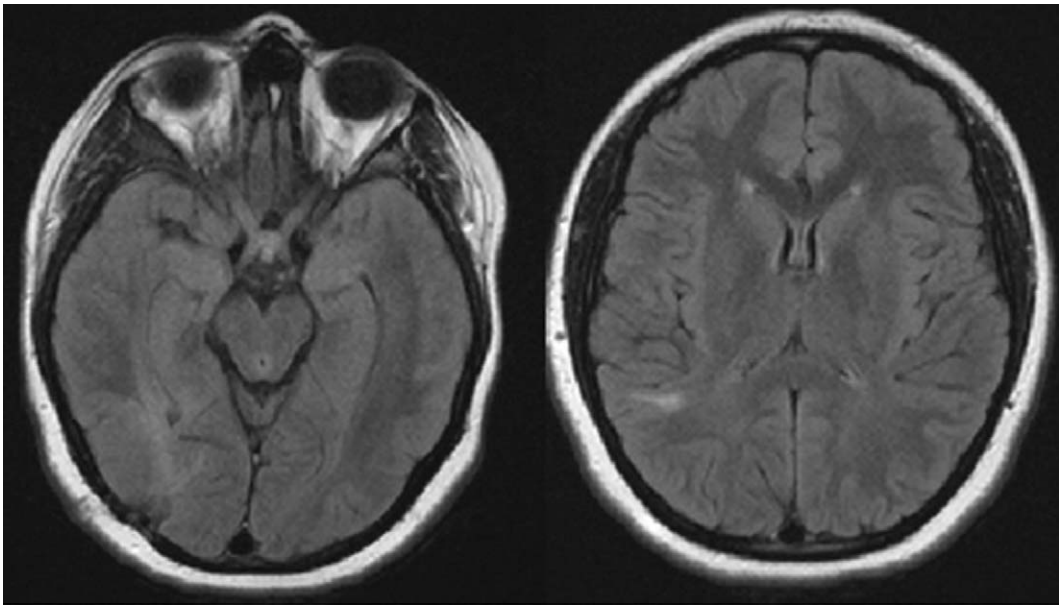

Figure 5. Magnetic resonance imaging 18 months after admission. FLAIR: near total resolution of the high signal intensity in the right hemispheric lesion.

established. There have been only 4 cases of central nervous system demyelination reported in the literature associated with the fairly new tetravalent vaccine against human papilloma virus.[21] Larger epidemiologic studies will be needed to confirm a role of the human papilloma virus immunization and demyelinating disease.

As has been demonstrated in prior reports, the brain biopsy in this case showed a primary inflammatory demyelinating process without axonal loss. Lymphocytes and macrophages were present within the plaque and in the perivenular spaces. These findings do not distinguish between multiple sclerosis, acute demyelinating encephalomyelitis, and their variants; a more subtle distinction may lie in the fact that in multiple sclerosis, inflammatory cells are generally present throughout the plaque rather than restricted only to the perivenular cuff, a feature that

Table 1. Reported Childhood Acute Chiasmal Neuritis in the Post-MRI Era

Citation	Etiology identified	Clinical presentation (age/gender)	Initial MRI	Follow-up MRI	Clinical follow-up
Purvin et al[3]	EBV	13/female: junctional field defect, and bitemporal superior quadrants defects	MRI 6 weeks after clinical onset is normal	Not available	Nine weeks later visual acuity and visual fields improved
Scott et al[2]	Lyme disease	10/female: clinical context of Lyme disease, visual acuity: Right eye light perception and left eye normal	Thickening with gadolinium enhancement of the right optic nerve and anterior chiasm	No enhancement, minimal enlargement after corticosteroid treatments	No change in visual function despite corticosteroids
Itzchak et al[4]	EBV	8/female: left optic neuritis 3 weeks after an upper respiratory infection	Infiltration of the left part of the chiasm	Not available	Marked improvement at 1 month, both disks have temporal pallor
Newman et al[15]	N/A	Case 4			
		18/female: decreased vision right eye, bitemporal visual fields defect	Mild enlargement of right side of optic chiasm	N/A	Right eye improved and left eye normal Visual fields: normal
	N/A	Case 6			
		16/female: impaired vision of the left eye, bilateral pale discs, right supero-temporal visual field defect and left central scotoma	Numerous T2-weighted MRI lesions, chiasm normal	N/A	N/A

NOTE: MRI, magnetic resonance imaging; EBV, Epstein-Barr virus; N/A, not available.

is more characteristic of acute demyelinating encephalomyelitis.[22]

It is possible that human papilloma virus was the precipitant for the demyelinating event in the patient presented here. It is tempting to speculate whether there may be a specific immune mechanism initiated with human papilloma virus not yet identified, which resulted in not only acute demyelinating encephalomyelitis but also in an unusual clinical course that resulted in persistent visual loss.

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