Letters to the Editor

Human Parvovirus B19 and juvenile systemic lupus erythematosus

Sirs,

Human Parvovirus B19 (HPV-B19) was first identified in 1975 (1) in asymptomatic blood donors, and was related to a pathological condition in 1981, when it was associated with the development of aplastic episodes in patients with sickle cell anemia. Subsequentely, HPV-B19 was reported as causing erythema infectiosum or 5th rash disease in childhood in 1983 (2).

A 12-year-old previously healthy girl presented with a 2-week history of pruritic maculopapular rash involving the trunk and extremities, myalgia and arthralgia, fatigue, spiking fever, arthritis involving both wrists and metacarpophalangeal (MCPs) joints and morning stiffness. Examination showed tenderness of the MCPs and wrists with swelling. Laboratory tests showed: blood count with normal red series, WBC 3,220/mm, and platelets 98,000/mm; ESR 70 mm (normal range, 0 to 20 mm/h). General biochemistry showed: normal GGT, GOT, GPT and CK, no urinary changes, negative RF, peripheral ANAs (+) 1/680, anti-DNA (+), antiSm (–), antiRo (–), antiLa (–), anticardiolipin (–), circulating anticoagulant (–),C3 60 (normal: 88-201) and C4 12 (normal: 16-47), negative serologic testing for hepatitis B and C, EBV and CMV viruses. Anti-HPV-B19 Ig M (+). No changes were observed in hand and chest X-rays. The echocardiogram was normal.

A possible SLE-like syndrome due to acute parvovirus B19 infection was diagnosed, and treatment was started with ibuprofen. The arthritis disappeared in 1 month.

Four months later, after sun exposure at the start of holidays at the beach, a rash appeared in the malar areas as well as oral aphthae, together with inflammatory signs in the wrists and MCPs. The laboratory tests were similar to the above, except for negative anti-HPV-B19 IgM and positive anti-HPB-B19 IgG. Treatment was started again with NSAIDs, with a poor response. Prednisone was added at a dose of 0.5 mg/kg/day, and the symptoms disappeared in 3 weeks; this treatment was slowly tapered. During the 32 weeks of follow-up, the girl has experienced 5 episodes of intermittent arthritis, oral aphthae, malar rash, and exacerbating of asthenia, with persistent leukopenia, thrombopenia, ANA(+) antiDNA(+) and hypocomplementemia in the laboratory tests. In the last 3 months, treatment with hydroxychloroquine was prescribed at a dose of 5 mg/kg/day, with no symptomatic relapse. The present treatment is prednisone at a dose of 5 mg/day and hydroxychloroquine at a dose of 5 mg/Kg/day, with no symptomatic relapse after this medical treatment was introduced.

The persistence of disease activity after more than 2 years leads us to suspect that this is a case of juvenile SLE in which HPV-B19 may have acted as a trigger. Infection by parvovirus B19 has been linked to various rheumatic signs. Up to 80% of adults with recent infection by PVB19 may show joint symptoms, as compared to 8% in patients under 20 years of age (3). SLE is a chronic autoimmune disease of unknown etiology that has been related to infection by PVB19 in different ways. One possibility is that an acute viral infection mimicking SLE can occur, with skin and joint symptoms, pancytopenia, hypocomplementemia and autoantibodies. The differential diagnosis may initially be difficult, but the self-limited course lasting a few months suggests a SLE-like syndrome caused by the virus (4). Secondly, infection by PVB19 can act as a trigger of true SLE in predisposed patients (5). Finally, infection by PVB19 can cause exacerbations in patients already diagnosed with SLE (6).

There are several well-documented cases of SLE-like syndrome and SLE triggered by HPV-B19 in adults (3), but few have been reported in children. A review of the literature reveals a total of 13 cases: 10 cases of SLE-like syndrome, one case of true SLE triggered by infection by PVB19, an exacerbation of a previously diagnosed SLE, and a neonatal SLE-like syndrome (4, 7-10). They were all girls, except for one, and the most common symptoms were fever, rash and arthritis. The laboratory changes include increased ESR, cytopenia, hypocomplementemia and the presence of autoantibodies. In all cases, the clinical signs were self-limited with symptoms usually subsiding before 18 months, except for the case of true SLE, where a chronic condition was established. The characteristics of these children are summarized in Table I.

In our patient, the diagnosis of SLE-like syndrome was initially considered, since the skin and joint symptoms, fever and immune changes, with antiPVB19 IgM antibodies, were consistent with an acute parvovirus infection, but the occurrence of relapses after 32 months of follow-up, with a change in serology to negative PVB19 IgM and positive IgG, led to a change in the diagnosis to SLE triggered by an infection with PVB19. Based on this diagnosis, treatment with hydroxychloroquine was started with a good response.

In conclusion, it should be recognized that acute parvovirus infection in children can cause a condition with clinical signs and serologic results similar to SLE. Thus, PVB19 infection should be considered in children with rash, fever, arthritis and immunological changes. In these cases, the measurement of specific IgM antibodies is the best way to show a recent infection. In other cases, such as the one reported here, PVB19 can start SLE in children. It would be interesting to perform a follow-up of large series of patients with PVB19 infection and clinical and serologic signs of SLE to accurately establish the role of the virus.

Table I.

Case	Gender	Age	Fever	Rash	Arthritis Arthralgias	ESR	ANA	Diagnosis	Reference
1	F	12	+	+	+	≠		1	7
2	F	13	+	+	+	≠	+	1	7
3	F	9	+	+	+			2	7
4	F	13	+	+	+	≠	+	1	7
5	F	days	-	+	-			3	8
6	F	15	+	+	+	≠	+	4	9
7	F	6	+	+	+		+	1	4,10
8	F	12	+	+	+		+	1	10
9	F	14	+	+	+		+	1	10
10	F	15	+	+	+			1	10
11	F	12	+	+	+	≠	+	1	10
12	M	15	+	-	+		+	1	10
13	F	15	+	+	+	≠	+	1	10

(1) SLE-like syndrome; (2) juvenile SLE; (3) neonatal SLE-like syndrome; (4) exacerbation of juvenile SLE.

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Myasthenia gravis: an unusual cause of diplopia in polymyalgia rheumatica

Sirs,

Polymyalgia rheumatica (PMR) is a clinical syndrome in elderly patients characterised by aching in the proximal portions of the extremities and torso, morning stiffness and evidence of systemic inflammation, such as an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein. PMR typically responds rapidly to low-dose prednisone. Giant cell arteritis (GCA) complicates the course of PMR in a varying proportion of patients (6% to 30%) (1). Ocular lesions in GCA include ischemic optic neuropathy (the most common ocular manifestation), retinal ischemic lesions and ophthalmoplegia, with or without diplopia which has been reported in approximately 12% of cases (2). We report here a case of a woman with PMR who developed diplopia as a consequence of myasthenia gravis (MG).

A 69-year-old woman previously diagnosed with knee osteoarthritis and monostotic Paget's disease of bone in the left tibia which started in June 2000 with aching and pain in the muscles of the neck, shoulders, lower back and hips, anorexia, malaise, a raised ESR (89 mm at the first hour), and C-reactive protein of 3.06 mg/dl, without headache, jaw claudication, or visual manifestations. Prednisone 15 mg daily was started with a favourable response and a progressive tapering of the dose was initiated.

She remained asymptomatic until February 2003, when she complained of diplopia. The patient was referred by her general practitioner to an ophthalmologist. After a complete evaluation that disclosed a normal fundus without signs of isquemic optic neuropathy, a cranial and orbital computer tomography scan and a neurophysiologic study were ordered. CT was normal but neurophysiologic study revealed an increased fatigability of the extraocular muscles with evidence of disease activity on routine muscle sampling (final mean of consecutive differences 56.1 ms). Antibodies against acetylcholine receptors were positive at a concentration of 7.40 nmol/L (normal range < 0.40 nmol/L). A biopsy of temporal artery was discarded when MG was diagnosed based on the neurophysiologic study and the presence of antibody anti-acetylcholine receptor. The patient was initially treated with oral prednisone 60 mg daily, with significant symptomatic improvement. After the diagnosis of MG, piridostigmine was started and the dose of glucocorticosteroid rapidly tapered. The patient remains asymptomatic with piridostigmine bromide 60 mg tid and oral prednisone at a dose of 7.5 mg qd.

A close relationship exits between GCAand PMR. Both conditions affect the same population of patients and frequently occur in the same individual. Due to the predominant involvement of branches of the carotid artery, visual symptoms and signs are common in GCA. Although the most common ocular symptom in GCA is visual loss, diplopia may be the first manifestation of GCA complicating PMR (3-6). In GCA, diplopia usually results from an ocular motor nerve paresis.

MG is a relevant cause of recent-onset diplopia in the general population (7). It is a condition caused by autoantibodies against the human nicotinic acetylcholine receptor, which results in impaired neuromuscular transmission and muscle weakness, either developing or becoming more evident with exertion. Although in cases of inappropriate control of the symptoms, immunosuppressive treatment (high-dose prednisolone) is indicated, the first-line treatment of MG consist of oral anticholinesterase agents (8, 9). Therefore differentiating the two conditions GCA and MG is critical to avoid unnecessary therapy with glucocorticosteroids. The present case emphasises that, although the first possibility in a patient with PMR who develops diplopia is GCA, other causes of ocular symptoms must be reasonably ruled out (Table I).

Table I. Causes of diplopia.

- Monocular diplopia
  - Optical problem
    - Refractive error
    - Keratoconus
    - Cataract
  - Psychogenic or functional
- Binocular diplopia
  - Myoneural junction
    - Myasthenia gravis
  - Restriction of extraocular muscles
    - Inflammation (orbital miositis)
    - Infiltration (thyroid ophthalmopathy or metastatic disease)
    - Entrapment (blow-out fracture of the orbital floor)
  - Disorders of the ocular motor nerves
    - The oculomotor nuclear complex (third nerve)
      - Aneurysms
      - Vascular disease (hypertension, atherosclerosis, diabetes mellitus, temporal arteritis)
      - Trauma and tumor (pituitary tumor, cavernous sinus meningioma, metastasis)
      - Parasellar mass lesions
      - Aberrant regeneration
    - Trochlear nerve (fourth cranial nerve)
      - Trauma
      - Vascular diseases (hypertension, atherosclerosis, diabetes mellitus).
      - Aneurysms (cavernous internal carotid artery or basilar artery).
      - Hydrocephalus
      - Sequelae to intracranial surgery
    - Abducens nerve (sixth nerve)
      - Infarction
      - Aneurysms
      - Tumor
      - Trauma
      - Leptomeningitis
      - Multiple sclerosis
    - Multiple ocular motor nerve palsies
      - Nasopharyngeal carcinoma
      - Granulomatosous inflammatory processes ("Tolosa Hunt" syndrome)
      - Lymphoma
      - Pituitary tumors
      - Meningiomas
      - Chordomas
    - Internuclear ophthalmoplegia
      - Brainstem glioma (in children)
      - Multiple sclerosis (in adults)

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