

# Mononeuropathy multiplex associated with acute parvovirus B19 infection: characteristics, treatment and outcome

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**Abstract** To describe the characteristics of peripheral neuropathy related to acute parvovirus B19 (B19V) infection. We reviewed clinical, electrophysiological and histological data of three patients with peripheral neuropathy and positive B19V detection (IgG, IgM and PCR) compatible with acute infection. The neuropathy fulfilled criteria for mononeuropathy multiplex (MM). It could be preceded by or concurrent with a limited purpuric eruption, but systemic manifestations were absent. The first neurological symptoms were always sensory and localized in a hand. Neuropathy was initially limited to a restricted sensory part of a nerve trunk territory. The course was subacute with successive and asymmetric injury of the limb and cranial nerves. Electromyographic study confirmed the

diagnosis of MM with multifocal asymmetric sensory and motor axonal loss in two patients, whereas the neuropathy was purely sensory and limited to two nerves in the other patient. Nerve biopsies showed no evidence of necrotizing vasculitis but, in one patient, revealed a lymphocytic perivascular infiltrate evocative of hypersensitivity vasculitis secondary to an infectious agent. Intravenous immunoglobulin (IVIg) was systematically administered. Long-term outcome was good but with incomplete sensory recovery and, for one patient, persistence of a functional disability. B19 V infection should be considered in the etiological assessment of MM, especially in the event of a progressive sensory disorder in the hands and a concomitant history of rash. IVIg may be an effective treatment for this inflammatory disorder.

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## Introduction

Human parvovirus B19 (B19V) infection is very common and usually asymptomatic. However, during its acute phase it may be associated with a wide spectrum of clinical manifestations, ranging from mild self-limiting erythema infectiosum in immunocompetent children to lethal cytopenias in immunocompromised patients and fetal hydrops or fetal death in primary infected pregnant women [2]. In adults, symmetric nondestructive polyarthritis may occur. It is also established that B19V infection may trigger autoimmune and/or inflammatory disorders, in which neurological manifestations have rarely been described. Peripheral nervous system manifestations occur more commonly in immunocompetent or elderly patients,

whereas central nervous system manifestations are usually reported among children [4]. Infection with B19V is considered to be a potential predisposing factor for the development of acute encephalitis [14], Guillain-Barré syndrome [8] or neuralgic amyotrophy [10].

The occurrence of authentic mononeuritis multiplex (MM) has rarely been described in the context of B19V-associated polyarteritis nodosa and papular purpuric gloves and socks syndrome [1, 3, 15]. We report here three cases of MM unambiguously associated with B19V infection in the absence of systemic features or restricted to a limited cutaneous eruption.

## Patients and methods

We included patients presenting with neuropathy and a serologic profile consistent with recent B19V infection during the period from January 2005 through December 2006.

Testing for B19V-specific IgG and IgM antibodies was performed using a commercial ELISA assay (Parvovirus B19 4th Generation, Biotrin, Dublin, Ireland) according to the manufacturer's recommendations. PCR detection of B19V DNA and DNA sequencing for genotype determination were performed as previously described [13].

## Results

The clinical features of the three cases are summarized in Table 1.

Diagnosis of the neuropathy, treatment and follow-up

### Case 1

A healthy 39-year-old man presented with a palpable purpuric eruption on both legs concurrent with painful paresthesia and numbness along the right fourth and fifth fingers, progressively spreading to the internal side of the right hand and forearm. Two weeks later he presented paresthesia and numbness of the left thumb with progressive extension to the left hand combined with motor weakness. At the time of neurological examination there was clinical evidence for sensory-motor involvement in left ulnar, left median, and right radial nerve territories, and decreased pinprick/vibration sensation in right ulnar, right internal cutaneous brachial, right saphenous and both sural and peroneal nerves. Electrodiagnostic features were indicative of a multifocal axonal neuropathy reflecting clinical findings. The skin biopsy of a purpuric lesion revealed small vessel vasculitis. The right sural nerve

**Table 1** Characteristics of three patients with peripheral neuropathy and parvovirus B19 infection

Patient	Age in years/sex	Cutaneous rash	First neurological symptoms	Course of neuropathy	Nerves clinically affected		EMG conclusions	Treatment
					S	SM		
1	39/m	Palpable purpuric eruption on legs	P/N 4th & 5th R fingers + progressive diffusion to ulnar nerve territory	Subacute (8–12 weeks)	L ulnar L median L radial	R ulnar R saphenous B sural B peroneal	SM axonal MM	C, IVIg
2	50/m	Nodular purpuric eruption with central necrosis of L arm and legs	P/N L index finger + progressive diffusion and motor weakness in median nerve territory	Subacute (2 weeks)	L median R sural	–	Pure sensory axonal MM	IVIg
3	40/w	–	P/N L index finger + progressive diffusion and motor weakness in median nerve territory	Subacute (8–12 weeks)	R sural L trigeminal (3rd branch)	R peroneal B median B ulnar B radial	SM axonal MM with marked axonal loss and active denervation	C, IVIg

P/N paresthesia/numbness, R right, L left, B bilateral, S sensory, SM sensory-motor, EMG electromyographic study, MM mononeuropathy multiplex, C corticosteroids, IVIg intravenous immunoglobulin

biopsy showed a great proportion of fibers undergoing axonal degeneration with no apparent vessel wall inflammation or fibrinoid necrosis.

Oral corticotherapy (prednisone, 1 mg/kg) was first introduced. After 1 month, in the absence of any neurological improvement, it was combined with monthly courses of intravenous immunoglobulin (IVIg). Because of a noticeable neurological and neurophysiological improvement, IVIg doses were discontinued after 18 courses. Outcome was good with a progressive improvement of sensory-motor symptoms. After 46 months of follow-up there was only a persistent but very mild weakness and numbness in both hands.

### Case 2

A 50-year-old man with no past medical history presented multiple infracentimetric nodular purpuric eruptions with central necrosis on the left arm and both legs. One week later he complained of painful paresthesia and numbness along the left forefinger with progressive spread to other fingers and the palm. After a few days he also complained of a tingling sensation in the right foot. Neurological examination and electrophysiological study were suggestive of a pure sensory axonal MM limited to left median and right sural nerve territories. Considering the mild clinical involvement, nerve biopsy was not performed. Biopsies of skin lesions showed T-lymphocytic perivascular infiltrates.

The patient received monthly courses of IVIg for 10 months. IVIg was discontinued after 12 courses. Outcome was initially marked by the transient occurrence of mild motor and sensory disturbances in the left ulnar nerve. However, after approximately 3 years of follow-up, the outcome was good with only a persistence of mild numbness in the left hand and the right foot.

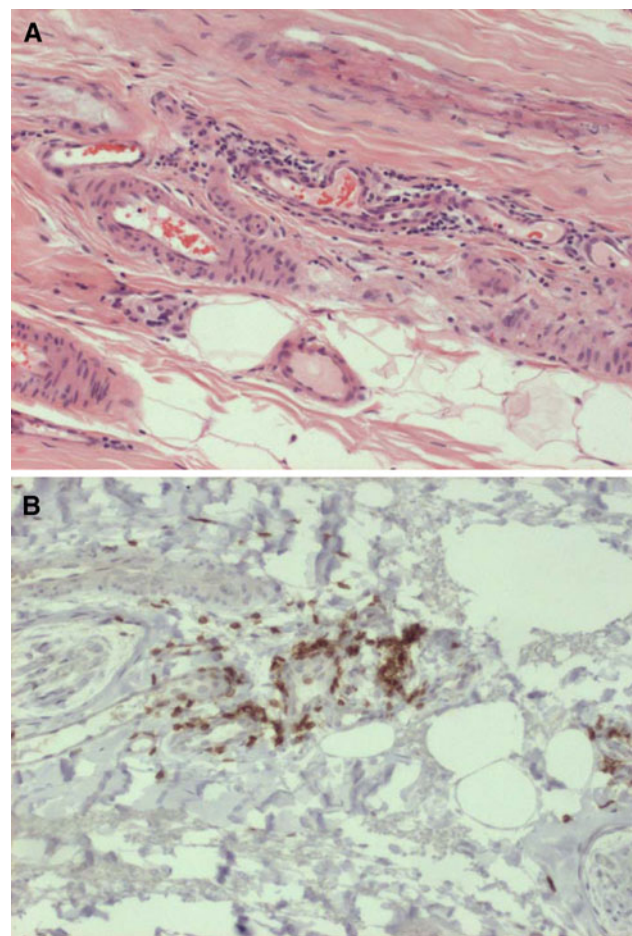
### Case 3

A 40-year-old woman, with a past history of asthma, experienced the onset of painful paresthesia along the left index finger with progressive spread to the first three fingers and simultaneous marked motor weakness. A few days later the same symptoms appeared on the right side with rapid confluence on both sides of the right hand. During the following weeks, the symptoms progressively became symmetric in the upper limbs, whereas asymmetric sensory and motor disturbances appeared in both legs. By the time of the neurological examination she had begun to feel numbness in the lower left portion of her face. Clinical and electrophysiological examination established a sensory-motor disorder in the right peroneal and both median, ulnar and radial nerves and a sensory disorder in the right sural

nerve and third branch of the left trigeminal nerve. Motor weakness in both hands was severe and associated with marked atrophy with marked active denervation on the electromyographic study. Nerve biopsy of the right sural nerve showed a high proportion of fibers undergoing axonal degeneration. Multiple pathologic cellular T-lymphocytic infiltrates were present in the interstitial tissue with a perivascular tropism, exclusively around vessels of microcirculation and predominantly in the epineurium and perineurium (Fig. 1). There was no apparent vessel wall inflammation and no fibrinoid necrosis.

First line therapy was based on prednisone. After 1 month, her clinical and electrophysiological status remained stable. It was then decided to add monthly IVIg. After one course there was a considerable clinical and well-correlated physiological improvement. IVIg therapy was continued once a month for 6 months and discontinued after seven courses.

After 30 months of follow-up, a severe sensory deficit and motor weakness persisted in the left hand.



**Fig. 1** Sural nerve biopsy specimen. **a** Hematoxylin and eosin stain: cellular lymphocytic infiltrates in interstitial tissue with perivascular tropism, exclusively around vessels of microcirculation; **b** immunomarking study: cellular infiltrates are T lymphocyte predominant

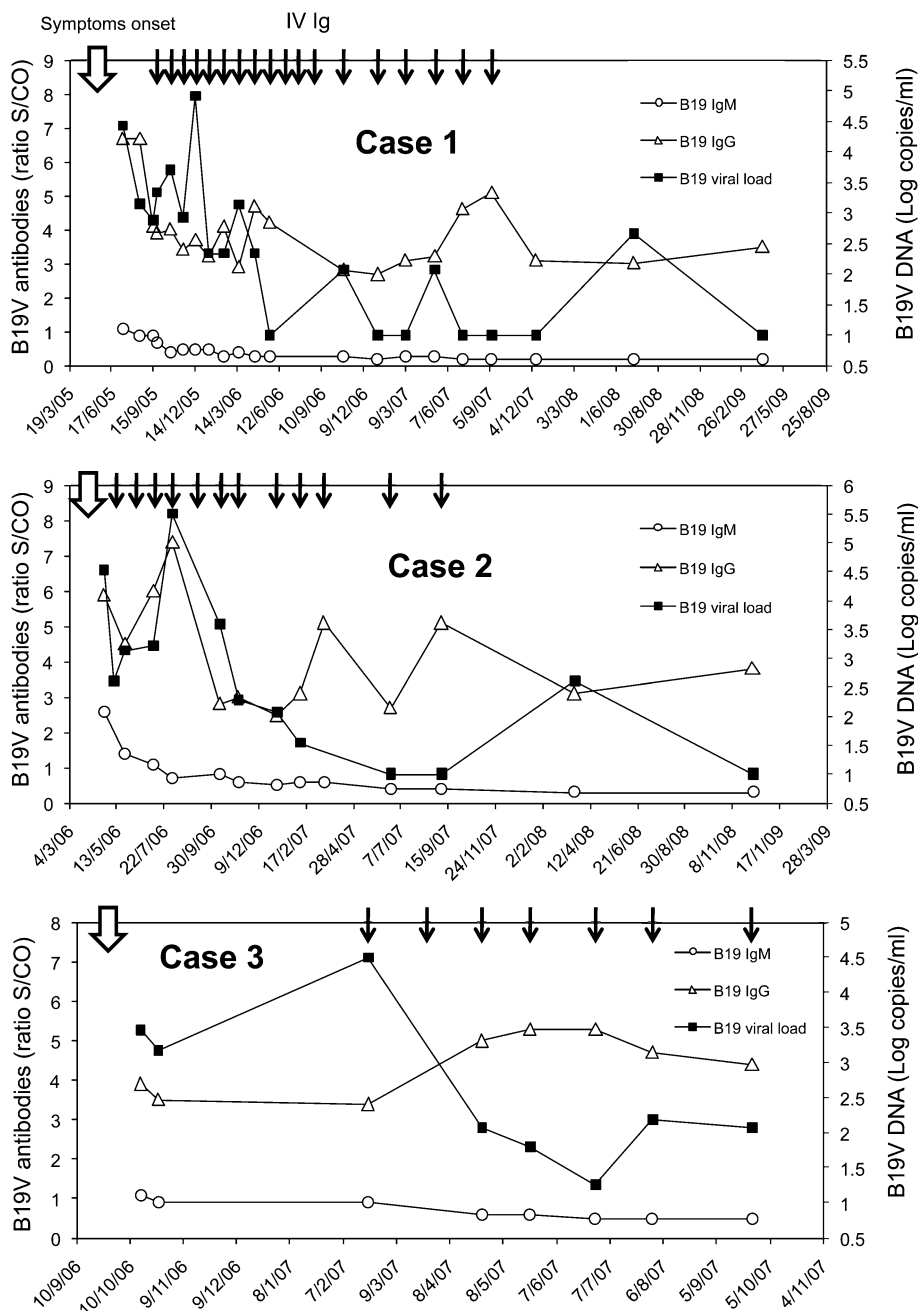
Biological features and diagnosis of B19V-associated neuropathy

The three patients had normal blood counts (except for transient nonclonal T-cell lymphocytosis in case 3), erythrocyte sedimentation rate, biochemical profile and serum ACE level, and had a negative 24-h proteinuria. Autoimmune profile including antinuclear factor, rheumatoid factor, anti-neutrophilic cytoplasmic antibodies and cryoglobulinemia was negative. Whole body CT-scan was normal. Human immunodeficiency virus, hepatitis C virus, hepatitis B virus, Herpes viridae (herpes simplex virus,

cytomegalovirus, herpes zoster virus and Epstein-Barr virus) and borrelia serologies were systematically tested and were negative or consistent with past infection. Cerebrospinal fluid study was normal (case 1, case 3) or had not been performed (case 2).

Details of the virological test results for B19V are summarized in Fig. 2. B19V infection was assessed both by serology, with detection of B19V-specific IgM antibodies and by PCR, with detection of B19V DNA in serum. B19 viruses isolated from all three patients were found to belong to genotype 1 according to the classification based on DNA sequence analysis [13].

**Fig. 2** Details of the virological test results for B19V





For each patient, the serologic B19V profile was marked by coexisting and persistent high levels of IgG and rapidly decreasing levels of IgM, indicating that patients were diagnosed at a late phase of an acute parvovirus infection. Positive PCR was initially detected and persisted at low levels for several months after the first detection.

## Discussion

The three patients were diagnosed with MM as they fulfilled the following criteria: (1) clinical history consistent with sequential multifocal motor and/or sensory involvement, (2) objective findings of multifocal motor and/or sensory involvement by neurological examination, and (3) electrophysiologic findings of axonal multifocal truncular motor and/or sensory involvement.

The diagnosis of a concurrent acute B19V infection was based on: (1) detectable B19V IgM antibodies already associated with high levels of B19V IgG at the time of the first serum sampling (1–2 months after symptoms onset); (2) decrease of IgM antibodies to undetectable levels during the serological follow-up; (3) PCR detection of B19V DNA in serum. In addition, the link between MM and B19V was also suggested by the negativity of the classical etiological assessment of MM and by the co-occurrence in two patients of a distal papulo-purpuric exanthema suggestive of acute B19V infection.

Development of the B19V-associated MM was subacute, with a progressive course. Extension and severity were unpredictable, ranging from pure limited sensory disorder to severe multifocal sensory-motor axonal loss with marked functional disability. The first symptoms were always sensory, localized in a hand and restricted to a limited part of the nerve territory. This unusual fascicular involvement spread progressively to the whole nerve trunk.

Samii et al. [12] reported three cases of acute bilateral median mononeuropathy following acute B19V with polyarthritis. However, they considered that the neuropathy had resulted from mechanical entrapment of median nerves in the context of wrist arthritis (carpal tunnel syndrome). Faden et al. described the occurrence of numbness and tingling of fingers associated with B19V infection in seven patients, but complete neurological, neurophysiological and histological examinations were not performed. However, this pattern is potentially indicative of multifocal neuropathy affecting upper limbs [5]. In one of the patients, the symptoms similarly affected toes on both feet and were combined with motor weakness.

Aguilar-Bernier et al. [1] recently described the coexistence of a neuropathy with cutaneous lesions but in the form of a gloves and socks syndrome associated with B19V. Gloves and socks syndrome is a typical exanthema

limited to the hands and feet that may be caused by B19V, with dysesthesia and/or paresthesia in the areas affected by exanthema being regularly observed. Clinical and physiological descriptions of their patient were strongly suggestive of MM with sensory-motor deficit in the right ulnar and tibial nerve territory and sensory disturbances in the left trigeminal nerve. Nerve biopsy was not performed, but besides the typical pathological features of gloves and socks syndrome, skin biopsy showed a lymphohistiocytic perineural infiltrate that may reflect the existence of lesions in the large nerve fibers.

The occurrence of a peroneal nerve mononeuropathy in one patient with B19V infection and a sensory disorder in the median and peroneal nerve in another patient has been reported in the context of several systemic manifestations such as polyarthralgia, myalgia, fever and weight loss [3, 15]. Nerve biopsy was not performed but skin biopsies confirmed the diagnosis of polyarteritis nodosa. In our patients, the pattern and development of the neuropathy did not suggest necrotizing vasculitis or nonsystemic vasculitic neuropathy, since vasculitis commonly affects lower limb nerves—especially the peroneal branch of the sciatic nerve—as the first manifestations of MM and results in early complete truncular sensory-motor deficit secondary to acute trunk nerve ischemia [11]. Indeed, in our cases pathologic features did not show evidence of necrotizing vasculitis, with absence of vessel wall inflammation and fibrinoid necrosis. In one patient the existence of multiple T-lymphocytic infiltrates with perivascular tropism was limited to the microcirculation. Although this infiltrates were not specific, they supported the hypothesis of a hypersensitivity vasculitis secondary to an infectious agent [6].

The way in which B19V is able to trigger inflammatory disorders is still not fully elucidated. Persistence of the viral infection, which may be observed even in immunocompetent individuals, may play a role in prolongation of the disorder [7]. Viral DNA is typically present in serum up to 6 months after onset of B19V infection [9]. Therefore, detection of viral DNA later than this time is suggestive of a persistent infection. Interestingly, in all three cases, B19V DNA remained detectable in serum for an unusually long period, indicating a possible evolution towards a persistent B19V infection. Thus, it may explain the transitory worsening of the MM following a period of neurological improvement observed in case 2. Similarly, Faden et al. [5] reported the intermittent recurrence of numbness and tingling over 1 year after acute B19V infection in three patients. This could suggest a specific mechanism for B19V-associated MM and provide a rationale for the treatment of such patients with IVIg, which usually contains high levels of B19 V-specific antibodies. IVIg appear to be effective as its introduction was systematically

followed by neurological and physiological improvement. However, its combination with steroids in two patients and the possibility of a spontaneous progressive recovery after acute nerve injury do not allow us to draw definite conclusions about the efficacy of IgIV in the case of B19V-associated MM.

Further epidemiological studies are required to establish the link between B19V and the neuropathy and to assess the frequency of B19V-related MM in comparison with other causes of MM. However, B19V infection should already be routinely considered in the etiological assessment of MM, especially in the event of initial sensory symptoms limited to a hand with concurrent rash, as this could lead to an early appropriate treatment with IgIV.

**Conflict of interest** None.

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