

Successful Intravenous Immunoglobulin Therapy in 3 Cases of Parvovirus B19–Associated Chronic Fatigue Syndrome

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Three cases of chronic fatigue syndrome (CFS) that followed acute parvovirus B19 infection were treated with a 5-day course of intravenous immunoglobulin (IVIG; 400 mg/kg per day), the only specific treatment for parvovirus B19 infection. We examined the influence of IVIG treatment on the production of cytokines and chemokines in individuals with CFS due to parvovirus B19. IVIG therapy led to clearance of parvovirus B19 viremia, resolution of symptoms, and improvement in physical and functional ability in all patients, as well as resolution of cytokine dysregulation.

Chronic fatigue syndrome (CFS) is characterized by severe debilitating fatigue that persists for ≥ 6 months and is accompanied by ≥ 4 of the following symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multijoint pain, new headaches, unrefreshing sleep, and postexertional malaise [1]. Although the causes of and risk factors for CFS are not well defined, epidemiological studies reveal that flulike illnesses suggestive of infective episodes precede the onset in the majority of cases. A major hypothesis for the pathogenesis of CFS is that an infectious trigger, such as the persistence of an infectious agent or other immune stimulus, may lead to a chronic activation of the immune system with abnormal regulation of cytokine production [2–5].

The resulting dysregulation in cytokine pathways may directly or indirectly contribute to the symptom complex associated with this disorder.

We have previously shown that acute symptomatic parvovirus B19 infection is associated with elevated circulating TNF- α and IFN- γ production [6] and with particular human leukocyte antigen class 1 and 2 alleles [7], and it may be followed by the development of CFS [8, 9]. Persistent parvovirus B19 infection is believed to result from a deficiency in the humoral immune response to this virus [10]. Intravenous immunoglobulin (IVIG) therapy has been shown to be effective for parvovirus B19–associated pure RBC aplasia in immunosuppressed persons [11] and also for several cases of other clinical manifestations in association with persistent parvovirus B19 infection, including 1 case of parvovirus B19–associated CFS [12]. The purpose of this study was to determine whether IVIG therapy could ameliorate the clinical symptoms and reverse the documented dysregulation in cytokine production in 3 cases of parvovirus B19–associated CFS.

Case reports. The patients are numbered 2, 8 and 32, as reported elsewhere [8, 9].

Patient 2, as described elsewhere [9], was a 42-year-old white woman who initially presented with an illness characterized by fever, skin rash, polyarthralgia, and fatigue coincident with an outbreak of parvovirus B19 infection at the school attended by her children. After a 5-month history of symptoms, she was tested in March 1998 and found to be positive for serum anti-parvovirus B19 IgM. This patient also reported a deterioration in memory and concentration, sore throat, painful aching muscles, new headaches, difficulty sleeping, unrefreshing sleep, postexertional malaise, an increased tendency to sweat, dizzy spells, and blurred vision. She had also experienced a sensation of heat in the soles of her feet and hot, dry eyes. Since the onset of acute parvovirus B19 infection, she had experienced persistent abdominal pain and diarrhea that remained undiagnosed despite extensive investigation, including colonoscopy, and she was being treated with carbamazepine and imipramine. Although she was able to continue working, her illness necessitated frequent time off from work, and eventually she had reduced her work commitment to part time. In addition, her social life had also been markedly curtailed by this illness. She had been treated with physiotherapy that had provided minimal benefit, and so she was referred for rheumatology assessment after a 24-month illness.

The findings of history, examination, and laboratory investigations performed immediately before commencement of

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IVIg therapy are summarized in table 1. At this time, the patient had had a 26-month history of fatigue, arthralgia, and other symptoms. During the examination, she appeared to be flushed and had no evidence of synovitis. She had pain on external rotation of her left hip, and 7 of 18 tender points were present. The findings of routine blood investigations, including a complete blood cell count, determination of urea and electrolyte levels, liver function tests, and determination of the erythrocyte sedimentation rate (ESR), were normal. The patient was found to be positive for serum parvovirus B19 DNA, serum anti-parvovirus B19 VP1/2 IgG and anti-parvovirus B19 NS1 IgG, and rheumatoid factor (RF), and she was found to be negative for leukocyte parvovirus B19 DNA and antinuclear antibody (ANA). The findings of Schirmer's test were normal. Skeletal radiography findings were normal.

In January 2001, the patient was admitted to hospital for IVIg therapy (Sandoglobulin; Novartis Pharmaceuticals) at a dosage of 400 mg/kg per day for 5 days, after which her symptoms resolved during the next 2 weeks, with a more gradual improvement during the next 2 months. At the time of this writing, her condition remains in remission. The patient subsequently returned to work without sick leave and was able to participate again in family and social activities that were not possible during her illness. Serial serum samples obtained at intervals from the onset of illness were tested for parvovirus B19 markers and cytokines.

Patient 8, as described elsewhere [9], was a 34-year-old Italian woman who was employed as a schoolteacher and was the mother of 2 young children. She presented in the summer of 1998 with a 3-week history of fever, skin rash, and polyarthralgia. She also complained of pain, a sensation of heat, and swelling in her elbows, shoulders, hands, back, neck, knees, ankles, and feet. Serum samples obtained in June 1998 were found to be positive for anti-parvovirus B19 IgM. After the acute phase, the arthralgia persisted in her elbows, knees, back, neck, fingers, and wrists; it occurred in regular bouts lasting 1–2 weeks and was associated with feeling feverish and shivery and with recurrence of cold sores. Fatigue was also a prominent feature of the acute phase and persisted throughout the follow-up period until June 2000. Additional symptoms included deterioration in memory and concentration, sore throat, painfully aching muscles, new headaches, difficulty sleeping, unrefreshing sleep, postexertional malaise, increased tendency to sweat, dizzy spells, and blurred vision. In April 2000, she presented with a 2-month history of palpitations; physical examination revealed bilateral exophthalmos and a diffuse goiter. Serum testing revealed a high level of thyroxine, which confirmed a diagnosis of hyperthyroidism. This illness was brought under control with propranolol and carbimazole therapy, and treatment with carbimazole (60 mg per day) was maintained. The fatigue and related symptoms had necessitated giving up her teaching ca-

reer, and she was able to socialize only rarely. She was referred for rheumatology assessment after a 24-month illness.

The findings of history, examination, and laboratory investigations performed immediately before commencement of IVIg therapy are summarized in table 1. At this time, the patient had had a 26-month history of fatigue, arthralgia, and other symptoms. During the examination, she was flushed and had no evidence of synovitis, and 7 of 18 tender points were present. The findings of routine blood investigations, including a complete blood cell count, determination of urea and electrolyte levels, liver function tests, and determination of the ESR, were normal. At follow-up, the patient tested positive for serum parvovirus B19 DNA and serum anti-parvovirus B19 VP1/2 IgG but negative for leukocyte parvovirus B19 DNA and anti-parvovirus B19 NS1 IgG. She also tested positive for RF and ANA (homogenous ANA titer, 300).

In January 2001, the patient was admitted to the hospital for IVIg therapy (Sandoglobulin) at a dosage of 400 mg/kg per day for 5 days. Within 2 weeks, she felt much improved, and during the next 2 months, she recovered completely. This treatment has enabled her to again participate in family and social activities that were not possible during her illness. Serial serum samples obtained at intervals from the time of onset of illness were tested for parvovirus B19 markers and cytokines.

Patient 32, as described previously [9], was a 46-year-old white salesman who presented in January 1998 with acute pain and swelling in his hands, knees, and ankles associated with a flulike illness; he tested positive for serum anti-parvovirus B19 IgM. Fatigue was present from the beginning of this illness. He had been in very good health before the development of this illness. During the next 2 years, he experienced joint pain in the hips, knees, ankles, wrists, and metacarpal joints. There was also intermittent swelling in the fingers. Fatigue had increased from the time of acute parvovirus B19 infection until it was necessary for him to sleep for several hours during the day. Although he was able to continue his work as a salesman, his social activities were severely restricted. He also reported a deterioration in memory and concentration, painful aching muscles, new headaches, difficulty sleeping, unrefreshing sleep, postexertional malaise, and an increased tendency to sweat. He was referred for rheumatology assessment after a 24-month illness.

The findings of history, examination, and laboratory investigations performed immediately before commencement of IVIg therapy are summarized in table 1. During examination, the patient was flushed and sleepy, with no evidence of synovitis, and 4 of 18 tender points were present. The findings of routine blood investigations, including a complete blood cell count, determination of urea and electrolyte levels, liver function tests, and determination of the ESR, were normal. Serological investigations revealed that the patient was positive for

Table 1. Symptoms, tender points, parvovirus B19 markers, and autoantibodies in 3 patients with persistent fatigue.

Characteristic	Patient		
	2	8	32
Sex	F	F	M
Age at onset of parvovirus B19 infection/ fatigue, years	42	34	46
Time since onset of acute parvovirus B19 infection, months	19 ^a	26	30
Deterioration in memory/concentration ^a	+	+	+
Sore throat	+	+	–
Tender cervical/axillary lymph nodes	–	–	–
Painful aching muscles	+	+	+
Arthritis			
Present	+	+	+
Duration, months	19 ^b	26	30
Joints affected	Hips, fingers, ankles, wrists	Elbows, knees, back, neck, fingers, wrists	Wrists, fingers, knees, hips, ankles
Joint swelling/redness	–	–	–
New headaches	+	+	+
Difficulty sleeping	+	+	+
Unrefreshing sleep	+	+	+
Post exertional malaise	+	+	+
Increased tendency to sweat	+	+	+
Dizzy spells	+	+	–
Blurred vision	+	+	–
Other symptoms	Prior Raynaud syndrome, ^c diarrhea, abdominal pain	Hyperthyroidism	–
Tender points	7	7	4
Diagnosis of fatigue	CFS	CFS	CFS
Serum parvovirus B19 DNA present	+	+	+
Leukocyte parvovirus B19 DNA present	–	–	–
Serum anti-parvovirus B19 VP1/2 IgG present	+	+	–
Serum anti-parvovirus B19 NS1 IgG present	+	–	–
Rheumatoid factor present	+	+	–
Antinuclear antibody titer present	–	300 ^d	–
HLA-DRB1 alleles present	01/04	0701/0801	0404/0404

NOTE. Fatigue persisted since the time of acute parvovirus B19 infection. All patients had fatigue for the entire follow-up period, the onset of which coincided with the onset of acute parvovirus B19 infection. CFS, chronic fatigue syndrome; HLA, human leukocyte antigen; +, present; –, absent.

^a Severe enough to result in significant reduction in occupational, educational, social or personal activities.

^b Intermittent.

^c Twenty years earlier.

^d Homogenous.

serum parvovirus B19 DNA but negative for leukocyte parvovirus B19 DNA, serum anti-parvovirus B19 VP1/2 IgG, anti-parvovirus B19 NS1 IgG, RF, and ANA.

In January 2001, the patient was admitted to the hospital for a 5-day course of IVIG (Sandoglobulin) at a dosage of 400 mg/kg per day. On day 2 of this treatment, he developed a

severe headache that lasted 48 h, and, on day 3, his joint pains began to improve. This improvement continued over the ensuing 2 weeks, by which time his fatigue had lessened. The arthritis was somewhat slower to resolve, but a marked improvement occurred at 3 months after treatment. At this time, his hips, knees, and ankles were virtually free of pain. This

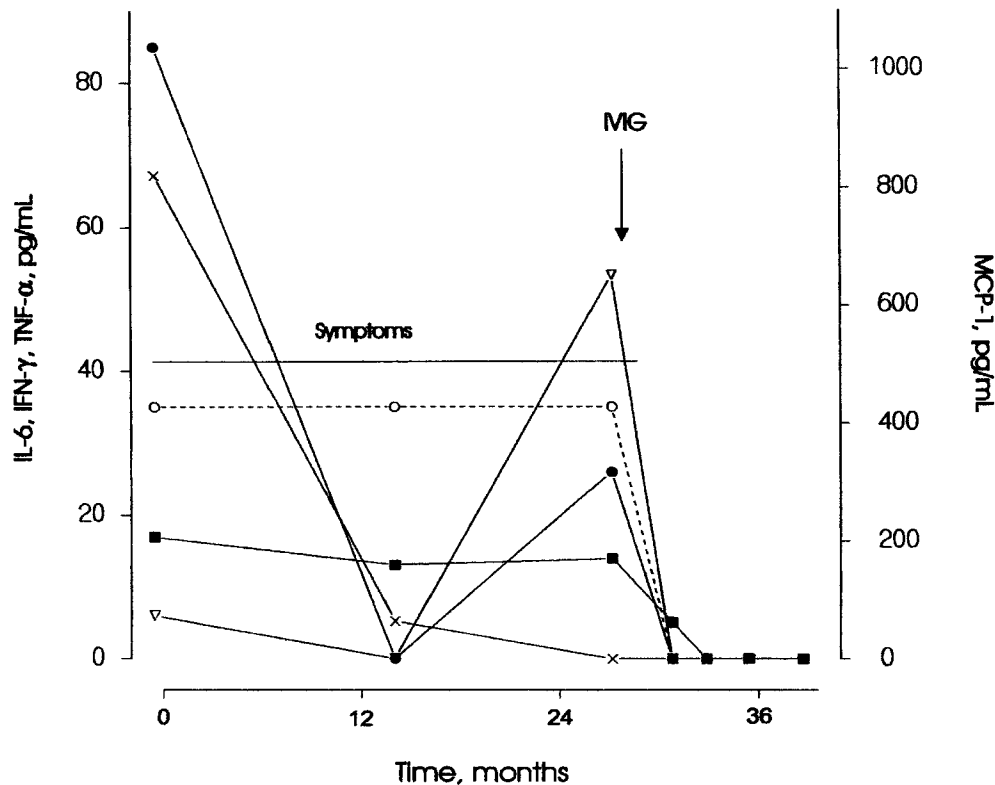


Figure 1. Time course of patient 2 with parvovirus B19-associated chronic fatigue syndrome (CFS) showing duration of clinical symptoms, serum viral DNA level (○), and levels of serum cytokines (IL-6 [x], TNF- α [●], IFN- γ [▽], and macrophage chemoattractant protein 1 [MCP-1; ■]) before and after the administration of intravenous immunoglobulin (IVIg).

improvement continued until he achieved a complete recovery. This treatment has enabled the man to participate again in family and social activities that were not possible during his illness. In particular, he could walk on flat surfaces without a stick. He no longer needed daytime naps after receiving treatment. At the time of this writing, his condition remains in remission. Serial serum samples obtained at intervals of 1–29 months from the onset of his illness were tested for parvovirus B19 markers and cytokines.

Materials and methods. Serum samples were tested for anti-parvovirus B19 VP2 IgM, by ELISA (Biotrin); anti-parvovirus B19 VP1/2 IgG, by Western blot test (Mikrogen); anti-parvovirus B19 NS1 IgG, by Western blot (Mikrogen); RF, by latex-particle agglutination (Fujirebio); and ANA, by indirect immunofluorescence. Nested PCR for detection of parvovirus B19 DNA was performed with DNA extracts of serum, as described elsewhere [9]. We have previously shown the sensitivity of this assay to be 1–10 genome copies [13].

A panel of cytokines was quantitated in serum specimens. These were measured in duplicate using the Bioplex Protein Array system (Bio-Rad), according to the instructions of the manufacturer. This is a novel, multiplexed, particle-based, flow cytometric assay that uses specific monoclonal antibodies linked to microspheres incorporating distinct proportions of 2 fluo-

rescent dyes. The assay is able to quantify several mediators in a single sample. Our assay was customized to detect and quantify IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, TNF- α , IFN- γ , granulocyte-macrophage colony stimulating factor (GM-CSF), and macrophage chemoattractant protein 1 (MCP-1). Mediators were included in this assay according to present knowledge of those upregulated during parvovirus B19 infection and those that may be implicated on the basis of present knowledge of the pathogenesis of parvovirus B19 infection. The limit of detection for these assays is <10 pg/mL on the basis of detectable signal greater than 2 SD above background (Bio-Rad). To standardize this cytokine testing system, we determined cytokine levels in 19 healthy persons.

Results. Mean cytokine levels in 19 healthy persons were as follows: IL-1 β , 0 pg/mL; IL-2, 0 pg/mL; IL-4, 0 pg/mL; IL-5, 0 pg/mL; IL-6, 2.14 pg/mL (range, 0–30.91 pg/mL); IL-8, 0 pg/mL; IL-10, 0 pg/mL; IL-13, 0 pg/mL; IFN- γ , 0 pg/mL; TNF- α , 1.62 pg/mL (range, 0–12.32 pg/mL); GM-CSF, 13.73 pg/mL (range, 0–67.26); and MCP-1, 0.83 pg/mL (range, 0–11.14 pg/mL).

In all cases, serum samples contained parvovirus B19 DNA that decreased to less than the limit of detection by our nested PCR assay after IVIG treatment (figures 1–3). The acute phase of each patient's illness began with a typical acute parvovirus

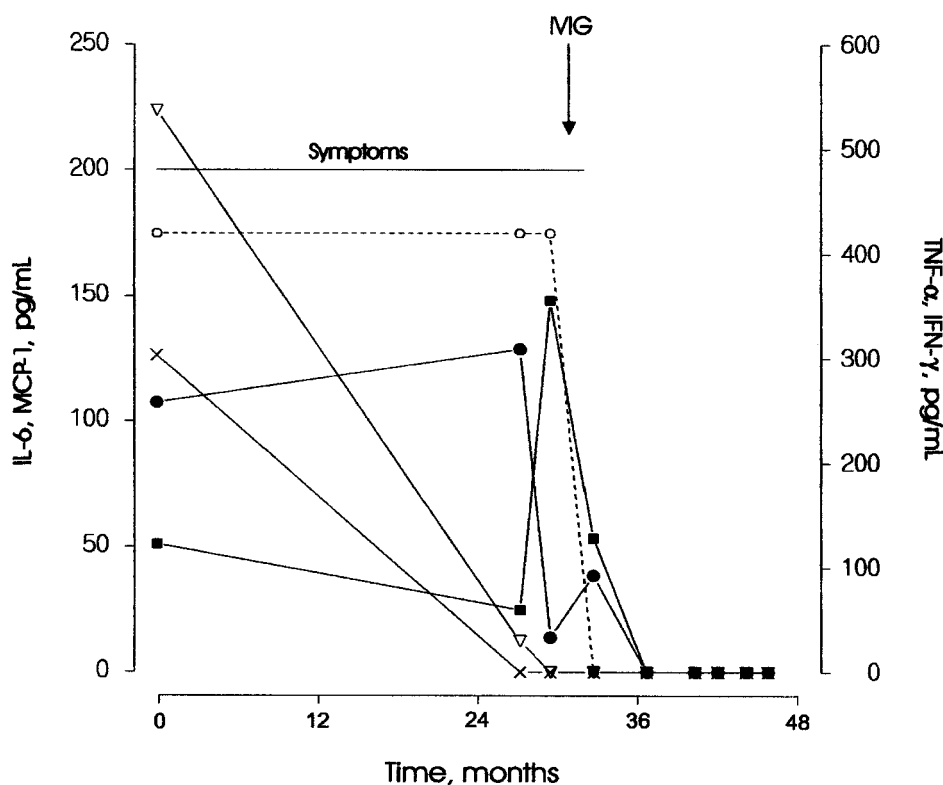


Figure 2. Time course of patient 8 with parvovirus B19-associated chronic fatigue syndrome (CFS) showing duration of clinical symptoms, serum viral DNA level (○), and levels of serum cytokines (IL-6 [x], TNF- α [●], IFN- γ [▽], and macrophage chemoattractant protein 1 [MCP-1; ■]) before and after the administration of intravenous immunoglobulin (IVIG).

B19 infection coincident with a positive test result for serum anti-parvovirus B19 IgM. Patients 2 and 8 mounted IgG responses to parvovirus B19; however, patient 32 did not switch class and tested negative for anti-parvovirus B19 IgG antibodies until he was treated with IVIG. In this patient, specific IgG antibodies were detected for the first time after completion of IVIG therapy.

Although many cytokines were quantified, only those that were significantly elevated above normal levels are discussed and included in figures 1–3. Before initiation of IVIG treatment, all patients had increased levels of MCP-1 and TNF- α . After IVIG therapy, MCP-1 and TNF- α levels decreased and were consistently less than the limit of detection for the Bioplex protein array system within 3–6 months of IVIG treatment in patients 2 and 8; however, the decrease was somewhat slower in patient 32. Patients 2 and 8 had intermittent increases in levels of IFN- γ and IL-6 during the disease phase, which decreased to baseline levels after the introduction of IVIG treatment. Patient 32 had a slightly different cytokine profile, with an elevated IL-4 concentration before receipt of IVIG therapy, which peaked 6 weeks afterward and then slowly returned to the baseline value. The decrease in the IL-4 concentration after administration of IVIG was similar to that noted for TNF- α and MCP-1. A smaller peak in the IL-2 level also occurred in

this patient after administration of IVIG treatment, coincident with the peak in the IL-4 level. An important limitation of the cytokine data was that antigen-specific responses were not assessed, and serum values may not accurately reflect cytokine concentration in the secondary lymphoid compartment. Further studies will be required to address these issues.

Discussion. IVIG treatment led to a significant improvement in symptoms and functional outcome in 3 patients with parvovirus-associated CFS. We hypothesized that IVIG therapy would be effective in this patient population for the following reasons. IgG antibody prevents in vitro infection of erythroid progenitor cells by parvovirus B19 [14], and volunteer studies have shown it to be protective [15]. Individuals with persistent parvovirus infection have a specific defect in humoral immunity to this virus [10]. Because parvovirus is a common infection in the population, with a seroprevalence of 60%–70% in blood donors [16], IVIG is a good means to neutralize antibodies [17]. Finally, IVIG has been shown to be an effective therapy for other clinical syndromes associated with persistent parvovirus infection, such as pure RBC aplasia in immunocompromised individuals [11] and in sporadic cases of parvovirus B19-associated arthritis [18], vasculitis [19], fetal anemia [20], meningoencephalitis [13], and CFS [12].

We have previously shown that parvovirus-associated CFS

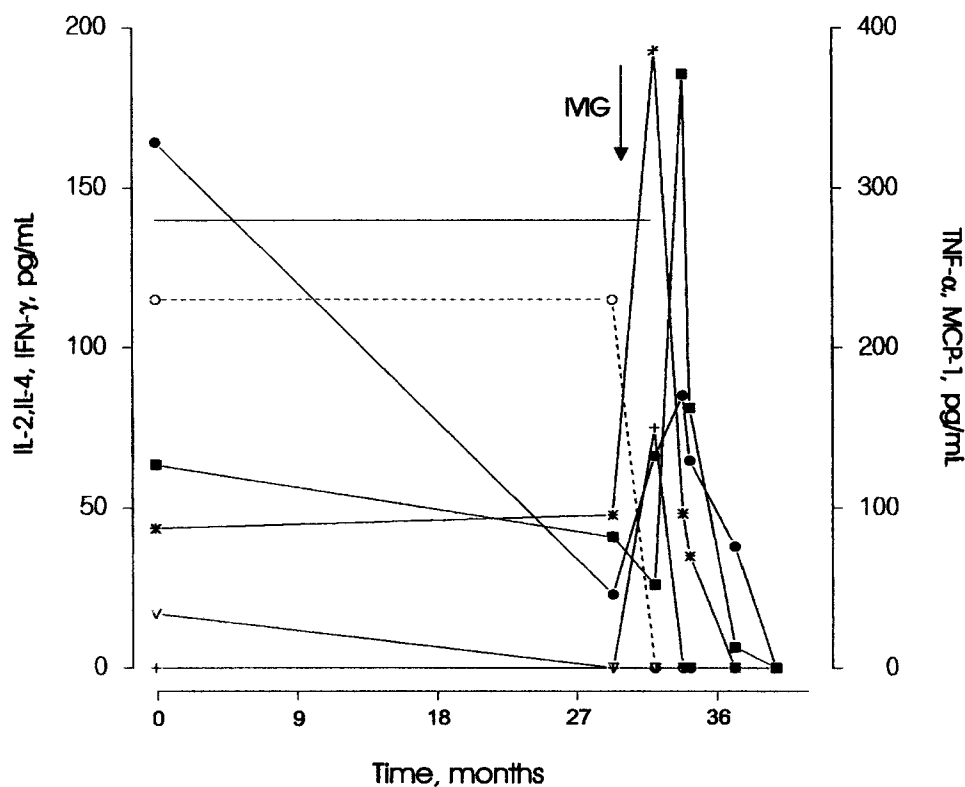


Figure 3. Time course of patient 32 with parvovirus B19-associated chronic fatigue syndrome (CFS) showing duration of clinical symptoms, serum viral DNA level (○), and levels of serum cytokines (IL-2 [+], IL-4 [*], IL-6 [x], TNF- α [●], IFN- γ [▽], and macrophage chemoattractant protein 1 [MCP-1; ■]) before and after the administration of intravenous immunoglobulin (IVIG).

was associated with increased circulating levels of TNF- α and IFN- γ [6]. In this study, all patients had persistent elevations of TNF- α and MCP-1 levels that returned to baseline values after IVIG therapy was administered. In one individual, parvovirus-specific IgG was detected for the first time after administration of IVIG treatment. This was associated with an isolated increase in levels of both IL-2 and IL-4 (figure 3), cytokines that are known to be important in immunoglobulin class switching [21, 22]. It has been suggested that detectable circulating IL-2 may protect against chronic symptoms after acute parvovirus infection [6] and may prevent parvovirus B19 infection of the human fetus [23]. Future studies are required to determine whether persistent parvovirus infection is associated with an antigen-specific defect in IL-2 production and production of other cytokines and whether such abnormalities may be corrected by IVIG therapy.

IVIG has been used to treat idiopathic CFS, and individual trials have shown benefit [24–26]. However, some trials do not show clinical benefit [27, 28], and a meta-analysis of all of the randomized controlled trials of IVIG therapy for idiopathic CFS was unable to determine whether this treatment had a clear-cut benefit [29]. One possible reason for the conflicting results of individual trials may lie in the heterogeneity of the population of patients with CFS; it is possible that some individuals

with idiopathic CFS may have persistent viral illnesses similar to parvovirus that are responsive to IVIG. However, another possibility is the heterogeneity of IVIG preparations. Notwithstanding, one goal for future studies is to determine what proportion of patients with idiopathic CFS have persistent parvovirus infection and whether screening for this should be routinely performed.

In conclusion, IVIG appears to be a promising treatment for parvovirus-associated CFS. It leads to a significant improvement in symptoms and to functional outcome and clearance of persistent viremia. Our findings provide support for the use of this therapy in parvovirus-associated CFS.

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