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REVIEW

Neurological aspects of human parvovirus B19 infection: a systematic review

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SUMMARY

Parvovirus B19 has been linked with various clinical syndromes including neurological manifestations. However, its role in the latter remains not completely understood. Although the last 10 years witnessed a surge of case reports on B19-associated neurological aspects, the literature data remains scattered and heterogeneous, and epidemiological information on the incidence of B19-associated neurological aspects cannot be accurately extrapolated. The aim of this review is to identify the characteristics of cases of B19-associated neurological manifestations. A computerized systematic review of existing literature concerning cases of B19-related neurological aspects revealed 89 articles describing 129 patients; 79 (61.2%) were associated with CNS manifestations, 41 (31.8%) were associated with peripheral nervous system manifestations, and 9 (7.0%) were linked with myalgic encephalomyelitis. The majority of the cases (50/129) had encephalitis. Clinical characteristic features of these cases were analyzed, and possible pathological mechanisms were also described. In conclusion, B19 should be included in differential diagnosis of encephalitic syndromes of unknown etiology in all age groups. Diagnosis should rely on investigation of anti-B19 IgM antibodies and detection of B19 DNA in serum or CSF. Treatment of severe cases might benefit from a combined regime of intravenous immunoglobulins and steroids. To confirm these outcomes, goal-targeted studies are recommended to exactly identify epidemiological scenarios and explore potential pathogenic mechanisms of these complications. Performing retrospective and prospective and multicenter studies concerning B19 and neurological aspects in general, and B19 and encephalitic syndromes in particular, are required. © 2014 The Authors. *Reviews in Medical Virology* published by John Wiley & Sons, Ltd.

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INTRODUCTION

Since its discovery in the 1970s of last century [1], human parvovirus B19 (B19) has been linked with a broad spectrum of clinical syndromes, including erythema infectiosum (EI), transient aplastic crisis, persistent infection manifesting as pure red cell aplasia in immunocompromised individuals, non-immune hydrops fetalis, and arthritis.

Less commonly recognized, but receiving increasing attention recently, are the neurological manifestations, a variety of which have been described in patients with either clinically diagnosed or laboratory-confirmed B19 infection. The last 10 years witnessed a surge of case reports on the association of B19 with neurological aspects. However, the literature on B19 infection and its association with neurological aspects continue to be heterogeneous, and epidemiological data on the incidence of B19-associated neurological aspects cannot be accurately extrapolated. Therefore, the

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Abbreviations used
AASM, acute autonomic sensory and motor neuropathy; B19, human parvovirus B19; CAT, computed axial tomography; CIs, confidence intervals; CTS, carpal tunnel syndrome; EEG, electroencephalogram; EI, erythema infectiosum; GBS, Guillain–Barré syndrome; IVIGs, intravenous immunoglobulins; ME, myalgic encephalomyelitis; MM, mononeuritis multiplex; MRI, magnetic resonance imaging; NIHF, nonimmune hydrops fetalis; PNS, peripheral nervous system; PRCA, persistent infection manifesting as pure red cell aplasia; PRISMA, preferred reporting items for systematic review and meta-analysis; TAC, transient aplastic crisis.

role of B19 in neurological diseases remains incompletely described and understood.

The pathogenesis of B19 infection is complex and variable, so it is likely that a combination of mechanisms contribute to the development of neurological manifestations [2], although there is a lack of detailed descriptions of autopsy reports.

The objectives of this systematic review are to search for cases of B19-related neurological aspects and identify the clinical characteristics of those patients that could be associated with B19 infection.

METHODS

A computerized search was conducted using all databases included in Web of Knowledge in addition to PubMed database. The search was performed combining the terms ('human parvovirus' or 'parvovirus B19' or 'B19' or 'erythema infectiosum') and ('neurologic complication' or 'neurological disorder' or 'neurological manifestation' or 'central nervous system' or 'peripheral nervous system' or 'a specific term for a specific neurological disorder') without language and time restrictions. The specific terms for neurological disorders used in the search were obtained from the website of National Institute of Neurological Disorders and Stroke [3], with a total of 442 disorders and manifestations. In addition, all cited references listed in the identified papers were hand-searched for other relevant articles. An article was considered for inclusion in the systematic review if it reported cases with B19 infection that presented with neurological manifestations. A case was considered eligible for the following reasons: (i) if data of age, sex, immune status, description of manifestations and investigation, treatment, and outcomes were presented and (ii) if B19 infection was diagnosed in the presence of B19 DNA or anti-B19 IgM specific antibodies in the serum or the CSF. Exceptions included cases with neurological manifestations associated with the presence of clinical presentation of EI while laboratory tests were not performed or available. The legitimacy behind that relies on the fact that B19 is the sole agent for EI. In the absence of B19 specific markers, other common B19-related clinical manifestations, such as transient aplastic crisis, persistent infection manifesting as pure red cell aplasia, nonimmune hydrops fetalis, and arthritis, were not considered as indicators of B19 infection because the latter is not their sole etiological agent. Cases of B19-associated neurological manifestations that result from intrauterine infection were also excluded. B19-associated myalgic encephalomyelitis (ME) cases were included because of the neurological classification of ME in the World Health Organization's International Classification of Diseases (ICD G93.3) but classified and labeled separately. Cases that did not fulfill the International Consensus Criteria of ME [4] were excluded. The computerized search was conducted for the last time on 30 June 2013. The preferred reporting items for systematic review and meta-analysis guidelines were followed [5].

Data were summarized using percentages and cross tabulations. Comparisons between subgroups were made using Fisher's exact tests. The 95% confidence intervals (CIs) for percentages were calculated using the Wilson method. All statistical analyses used the conventional two-sided 5% significance level and were carried out using SPSS version 20 and CIA version 2.0.

RESULTS

As shown in Figure 1, the search using Web of Knowledge databases identified 998 publications, whereas PubMed database search identified 903 publications, with a combined search result of 1065 publications. A scrupulous analysis resulted in 89 eligible articles [6–94] describing the history of 129 patients, published between the years 1970 and 2012, which were further evaluated.

Seventy nine of the eligible cases (61.2%) were associated with CNS manifestations (Table 1), whereas 41 (31.8%) were associated with peripheral nervous system (PNS) manifestations (Table 2), and nine cases (7.0%) were linked with ME (Table 3). Many of the cases (50/129) had encephalitis, encephalopathy, or meningoencephalitis. The patients age ranged from 1 day to 75 years; median age of 12.5 years, with 70 (54.3%) children (<18 years) and 59 (45.7%) adults (≥18 years). The male-to-female ratio was 4 : 5 (55.8% female). One hundred cases (77·5%) were immunocompetent, whereas 29 cases (22.5%) were patients with suppressed immune status.

Clinical features of B19-associated encephalitis, encephalopathy, and meningoencephalitis cases were subject to comprehensive analysis in this review because many of the B19-associated neurological aspects were cases belonging to this category. For readers who are interested in other B19-related neurological aspects, they should refer to Tables 1–3 and to the Discussion Section of this review.

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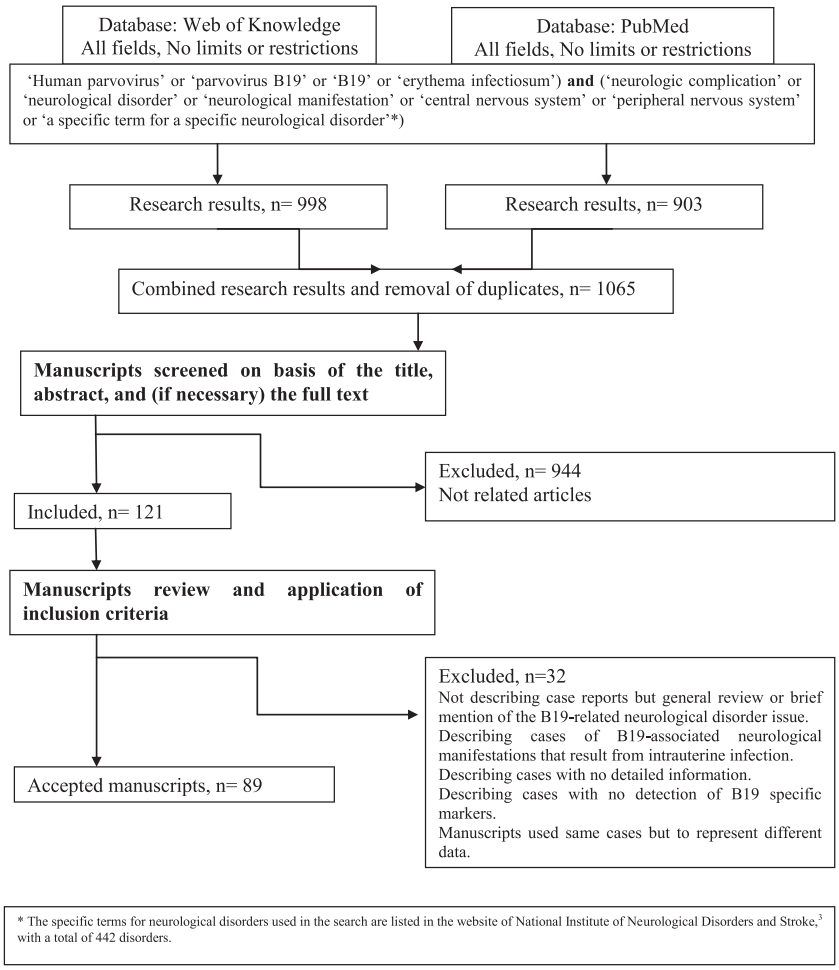

Figure 1. Flow diagram of information through the different phases of the review

B19 and encephalitis, encephalopathy, and meningoencephalitis

Fifty cases of encephalitic syndromes were found and reviewed [6–39], representing 63.3% of B19-related CNS cases and 38.8% of total B19-related neurological cases currently found in the literature (Table 1). In most of these cases (33/50), B19 was sought after other possible pathogens were proved to be negative, and the etiological cause was not determined. In addition, B19 was investigated in these cases because of the appearance of B19-related symptoms or merely because of a suspicion of B19 infection. This association was confirmed by the detection of at least one specific marker for B19 infection, with the exception of two cases of encephalitis associated with EI prior to the recognition of the etiological role of B19 in this disease [6,7]. However, 12 cases were identified during two retrospective studies of 43 and 282 patients, respectively, with etiologically undiagnosed neurological symptoms and with no sufficient clinical information to support the detection of a recent B19 infection [14,16]. Four more cases were detected in another retrospective study that targeted 346 patients with aplastic crisis [19]. An additional case was detected during a screening program of 1572 sera from hospitalized pediatric patients with various presentations submitted for viral investigation [8].

Analysis of CSF for cell count and protein and glucose concentrations varied according to the cases. From those who were subject to CSF analysis, 19 cases had normal white cells count, whereas 21 cases had raised count, 15 had normal protein concentration whereas 16 had higher concentration, and 23 had normal glucose concentration whereas only two had lower concentrations.

Table 1. Cases of B19 infection and manifestations related to the central nervous system

Case No. (Ref)	Age / Sex	Immune status	Neurological disorders	Other associated disorders	B19 related symptoms			B19 markers in serum			B19 markers in CSF			Other CSF tests ∞			Treatment ¥	Outcome	
					Rash	Anaemia	Arthralgia	IgM	IgG	DNA	IgM	IgG	DNA	White blood Cells count	Protein (mg/dl)	Glucose (mg/dl)		Neurological sequelae	Death
1 (6)	8y/M	C	Encephalitis	None	+ (Pro NM)	-	+	NA	NA	NA	NA	NA	NA	↑ (37, 100% L)	↑ (45)	N (58)	NS	Weakness clonus	-
2 (7)	9m/M	C	Encephalopathy Seizures	None	+ (With NM)	-	+	NA	NA	NA	NA	NA	NA	N (0)	N (47)	N (58)	NA	Psycomotor retardation	-
3 (8) †	8y/F	C	Encephalopathy Convulsions	None	-	+ (Post NM)	+ (Post NM)	+	ND	+	NA	NA	NA	NA	NA	NA	Spontaneous cure	-	-
4 (9)	5y/F	C	Encephalopathy Convulsions	None	+ (Post NM)	-	-	+	+	+	ND	ND	+	N	↑	NA	Spontaneous cure	-	-
5 (9,10)	5y/F	C	Encephalopathy Convulsive status-epilepticus	None	+ (Pro NM)	-	-	+	+	+	ND	ND	-	↑ (9, 100% L)	↑ (46)	NA	Anti-epileptics (Pentobarbitone Valporic acid Primidone)	Mental retardation	-
6 (11)	5y/M	C	Encephalitis Convulsions	Hepatitis	NK	NK	NK	+	+	+	-	-	+	N	↑ (147)	NA	NA	-	-
7 (12)	58y/F	S	Encephalitis Optic neuritis Cranial nerve palsies Aphasia Seizure	Lymphoma	-	-	-	+	+	-	-	+	+	N	N	N	NA	-	+
8 (13)	9y/M	C	Encephalopathy	None	+ (With NM)	-	-	+	+	+	ND	ND	-	NA	NA	NA	NA	-	+
9 (13)	7y/M	C	Encephalopathy	None	+ (With NM)	-	-	+	+	+	ND	ND	-	NA	NA	NA	NA	-	+
10 (13)	5y/F	C	Encephalopathy	None	+ (Post NM)	-	-	+	+	+	ND	ND	-	NA	NA	NA	NA	-	-
11 (14) †	4y/M	C	Encephalitis Seizures	None	+ (Post NM)	-	-	+	+	+	-	-	+	N	N	N	NS	-	-
12 (14) †	4y/M	C	Encephalitis	None	-	-	-	+	+	+	-	-	+	N	↑ (126)	↓ (12)	NS	Spastic quadriplegia	+
13 (15)	67y/F	C	Meningoencephalitis Ataxia	None	-	+	-	-	+	-	-	+	- €	↑ (117, 97% Mo)	↑ (1735)	↓	IVIG Steroids √ (MPDN, PDN)	-	-
14 (16) †	2m/M	C	Encephalitis Seizures	Conjunctivitis URT infection	-	-	-	+	+	-	-	-	+	NA	NA	NA	Steroids √ IVIG √	-	-
15 (16) †	2y/M	S	Encephalitis Pyrexia	Relapsed acute lymphoblastic leukaemia	-	-	-	NA	NA	NA	-	-	+	N (2, 100% Mo)	NA	NA	NA	Cognitive deficit	-
16 (16) †	2y/F	S	Encephalitis Tonic/clonic seizures Ataxia	Hepatitis	-	+	-	NA	NA	NA	-	-	+	N (1)	NA	NA	NA	-	-
17 (16) †	6y/F	S	Encephalitis	Cockayne's syndrome Multi-organ failure	-	-	-	NA	NA	NA	-	-	+	NA	NA	NA	NA	- *	+
18 (16) †	9y/M	C	Encephalitis Tonic/clonic seizures	Thrombocytopenia Cervical lymphadenopathy	-	+	-	+	-	+	-	-	+	NA	NA	NA	Anti-epileptics (phenytoin, Clonazepam) Antibiotics Antiviral	Cognitive deficit Convulsions episodes	-
19 (16) †	13y/F	C	Encephalitis	Liver failure Crigler–Najjar syndrome	-	-	-	NA	NA	NA	ND	ND	+	NA	NA	NA	Anti-epileptic √ (Barbiturates)	-	+
20 (16) †	13y/M	C	Encephalitis Hemiparesis Ataxia	None	-	-	-	NA	NA	NA	ND	ND	+	N (0)	N (40)	N (63)	Spontaneous cure	-	-
21 (16) †	15y/F	C	Encephalitis	None	-	-	-	NA	NA	NA	ND	ND	+	↑ (60 100% L)	↑ (300)	N (48)	Antibiotics Antiviral	Cognitive deficit	-
22 (16) †	1d/F	S	Encephalitis	Enterocolitis Patent ductus arteriosus Hepatitis Surfactant-deficient lung disease Osteopenia of immaturity Valgus leg deformity	-	-	-	+	+	+	+	-	+	N (14)	NA	NA	NA	Significant delayed development	-
23 (16) †	1d/F	S	Encephalitis	Ventricular septal defect Atrial septal defect Patent ductus arteriosus Poor respiratory drive Obstructive jaundice Turner's syndrome	-	+	-	NA	NA	NA	-	-	+	N (13)	NA	NA	NA	-	+
24 (17)	3m/F	S	Encephalopathy Opsoclonus	Severe combined Immunodeficiency Bone marrow transplant	-	+	-	ND	ND	+	ND	ND	-	↑ (100% L)	↑	NA	IVIG Steroid (MDPN) √ Antiviral	Motor delay	-
25 (18)	27y/F	C	Encephalopathy Prolonged status-epilepticus	None	+ (Pro NM)	-	-	+	+	-	ND	ND	ND €	↑ (41, 99% Mo)	N (34)	N (73)	Antiviral Anti-epileptics (phenytoine Phenobarbital Carbamazepine)	- (Slow recovery)	-
26 (19)†	8y/F	S	Encephalitis Tonic/clonic seizures Transient cortical blindness	Sickle cell anaemia Nephrotic syndrome Pneumonia	-	+	-	+	+	+	ND	ND	ND	↑ (600)	NA	NA	NS	-	-
27 (19) †	8y/M	S	Encephalitis Seizures	Sickle cell anaemia Nephrotic syndrome Acute chest syndrome	-	+	-	+	+	+	ND	ND	ND	↑ (21)	NA	NA	NS	-	-
28 (19) †	12y/F	S	Encephalitis Focal seizures of right arm Tonic/clonic seizures Transient cortical blindness	Sickle cell anaemia Acute chest syndrome	-	+	-	+	+	+	ND	ND	ND	↑ (7)	NA	NA	NS	-	-
29 (19) †	14y/M	S	Encephalitis Tonic/clonic seizures	Sickle cell anaemia	-	+	-	+	+	+	ND	ND	ND	↑ (37)	NA	NA	NS	-	-
30 (20)	19y/M	C	Meningoencephalitis Generalized convulsion	Parotitis Progressive liver dysfunction Concomitant mumps infection	-	-	-	+	+	+	ND	ND	-	↑ (24, 100% Mo)	↑ (81)	N	Antibiotics Antiviral IVIG √ Steroid (DXM) √	-	-
31 (21)	13y/F	S	Encephalopathy CNS vasculitis	Sβ°Thalassemia / aplastic crisis	-	+	-	+	+	-	-	+	ND	N	N (31)	N (79)	Antibiotic Steroids √	-	-
32 (22)	33y/M	S	Focal encephalitis Apraxia Dysphasia Aphasia	HIV under HAART treatment Immune restoration disease (IRD) Chronic hepatitis C	-	+	-	ND	ND	+	-	-	+	N	↑ (62)	N	IVIG Stopping HAART	Persistent dyspraxia	-
33 (23)	12y/M	S	Recurrent encephalopathy Seizures Hemiparesis CNS vasculitis	Renal transplant	+ (Pro NM)	+	-	+	-	+	ND	ND	ND	↑ (30, 100% L)	N	NA	IVIG √	-	-
34 (24)	10y/F	C	Meningoencephalitis Refractory status epilepticus	None	-	-	-	+	-	ND	-	-	ND	↑ (100,100% Mo)	↑ (51)	N	Anti-epileptics (Pentobarbital, Valporic acid, Midazolam) IVIG Steroids √ (MPDN, PDN)	-	-
35 (25)	8y/F	C	Choreaencephalopathy	None	-	+	-	+	+	+	ND	ND	+	N	N	N	NS	-	-
36 (26)	9y/M	S	Encephalitis Seizures	Renal transplant	-	+	-	+	-	+	-	-	ND	↑ (20)	↑ (72)	NA	Antiviral Antibiotic Steroid (DXM) Anti-epileptics (Diazepam, Phenobarbital, Clonazepam)	-	-

(Continue)

Table 1. (Continued)

37 (27)	68y/M	C	Encephalitis Seizures	Pneumonia	+ (Pro NM)	-	+	+	ND	ND	ND	ND	+	N (1, 100% L)	NA	NA	Antiviral Antibiotics IVIG	Mild language difficulties	-	
38 (28)	28y/M	C	Encephalitis	None	-	-	-	+	+	+	ND	ND	-	N	N	N	IVIG √	-	-	
39 (29)	15m/F	C	Encephalitis Seizures decreased level of consciousnc	Hepatitis	-	+	-	+	+	ND	NA	NA	NA	NA	NA	NA	NA	-	-	
40 (30)	36y/F	C	Meningoencephalitis Neuropathies	None	-	+	-	+	+	+	-	-	+	↑ (370, 90% L)	↑ (93)	N (55)	Steroids (DXN, MPDN) IVIG √ Pregabalin	-	-	
41 (31)	9y/F	C	Encephalopathy	Hereditary spherocytosis Aplastic crisis	+ (Post NM)	+	-	-	+	+	ND	ND	+	N (4)	N (11)	N (56)	Steroid (DXN) √ Mannitol	-	-	
42 (32)	39y/M	S	Encephalitis Nystagmus Diplopia	HIV under HAART treatment	-	+	-	+	+	+	ND	ND	ND	↑ (15, 100% L)	↑ (111)	N (44)	NS	-	-	
43 (33)	75y/M	C	Meningoencephalitis Disturbance of consciousness	Predominating psychiatric symptoms	-	-	-	-	+	-	-	-	+	↑ (210, 95% L)	↑ (242)	N (74)	Antibiotic Antiviral	-	-	
44 (34)	4y/F	C	Encephalitis Ataxia Dysmethria Dysarthria	None	-	-	-	-/+	-	+	-	-	+	↑ (40, 100% L)	N	N	IVIG √ Steroid (DXN) √	-	-	
45 (35)	1y/M	C	Encephalopathy Chorea	None	-	-	-	+/-	-	/+ ND	ND	ND	+	N (1, 100% L)	N (19)	N (75)	Antiviral Steroids (PDN) IVIG √	-	-	
46 (36)	2y/M	C	Encephalopathy Chorea	None	-	-	-	+	-	ND	NA	NA	NA	NA	NA	NA	Anti-epileptic (Clonazepam)	- (Slow recovery)	-	
47 (36)	2y/F	C	Encephalopathy Chorea	None	-	+	-	+	-	ND	ND	ND	ND	↑ (32, 60% Ne, 40% L)	N	N	Anti-epileptic (Clonazepam)	Global developmental delay (Slow recovery)	-	
48(37)	9y/F	C	Encephalopathy	Glomerulonephritis	+ (With NM)	+	-	+	+	+	ND	ND	+	N (4)	N (27)	N (55)	NS	-	-	
49 (38)	3y/M	C	Encephalitis	None	+ (Pro NM)	-	-	+	-	+	ND	ND	+	↑ (10)	N	N	Anti-epileptic Antiviral	-	-	
50 (39)	5y/F	C	Encephalopathy Cerebellitis	None	+ (Post NM)	-	-	+	+	+	ND	ND	+	↑ (229, mainly Ne)	↑ (144)	N (56)	Steroids Antibiotics Antiviral	Slurred speech Intention tremor	-	
51 (40)	13/M	S	Meningitis	Sickle cell anaemia	-	+	-	+	-	ND	NA	NA	NA	↑ (13, 83% L)	N	N	NS	-	-	
52 (41)	7y/F	C	Aseptic meningitis	None	+ (Pro NM)	-	-	+	+	ND	+	+	ND	↑ (339, 91% Mo)	↑ (71)	N (66)	Spontaneous cure	-	-	
53 (42)	7y/M	C	Aseptic meningitis	None	+ (Pro NM)	-	-	+	+	+	ND	ND	+	↑ (112, 61% Ne)	↑(58)	N (60)	Spontaneous cure	-	-	
54 (43)	35y/M	C	Meningitis	None	-	+	-	+	+	+	ND	ND	+	N (3, 66% Mo)	N (23)	N (78)	NS	-	-	
55 (44)	20d/F	C	Aseptic meningitis	None	- #	+	- #	+	+	ND	ND	ND	ND	↑ (861, 57% L)	N (54)	N (49)	IVIG Antibiotics	-	-	
56 (45)	26y/F	S	Aseptic meningitis	Sickle cell anaemia Denied blood transfusion	-	+	-	+	+	+	ND	ND	+	↑ (10, 100% L)	N (22)	N (84)	NS	-	+	
57 (46)	17y/F	C	Aseptic meningitis	None	-	-	-	+	+	-	ND	ND	+	↑ (253, 95% L)	↑ (210)	N (43)	Spontaneous cure	-	-	
58 (47)	2y/F	S	Meningitis Seizures	Lymphocytic leukaemia	-	+	-	+	-	+	ND	ND	+	↑ (32, 78% L)	N (28)	N (41)	NS	-	-	
59 (16) †	2m/M	C	Meningitis	Upper respiratory tract infection	-	+	-	+	+	+	+	+	+	N (13, 80% Mo)	NA	NA	Antibiotic	-	-	
60 (16) †	6m/M	S	Meningitis	Erythrophagocytosis Hepatosplenomegaly	-	+		NA	NA	NA	-	-	+	↑ (75, 90% L)	↑ (2800)	↓ (38)	Antiviral Antibiotics	-	+	
61 (48)	6y/M	C	Aseptic meningitis	None	+ (With NM)	-	-	+	-	ND	ND	ND	ND	N	N	N	Antibiotic	-	-	
62 (49)	8y/F	C	Meningitis	Hepatitis Hepatosplenomegaly Parotitis	-	-	-	+	+	ND	ND	ND	ND	N	N	N	Antibiotic	-	-	
63 (50)	2y/M	C	Cerebellar ataxia Nystagmus		+ (With NM)	-	-	+	+	+	-	-	-	↑ (9)	N (8)	N (65)	Spontaneous cure	-	-	
64 (19)†	3y/M	S	Stroke (R hemiparesis) Seizures Aphasia	Sickle cell anemia	-	+	-	+	ND	ND	NA	NA	NA	0	NA	NA	NS	Mild hemiparesis 20y later Aphasia	-	
65 (19)†	4y/M	S	Stroke (L hemiparesis) Seizures	Sickle cell anemia	-	+	-	+	+	ND	NA	NA	NA	NA	NA	NA	NS	Recurrent L hemiparesis after 6 months Complete resolution	-	
66 (19)†	6y/M	S	Stroke (R hemiparesis) Seizures	Sickle cell anemia	-	+	-	+	ND	+	NA	NA	NA	0	NA	NA	NA	Recurrent hemiparesis	+	
67 (19)†	8y/M	S	Stroke (L hemiparesis)	Sickle cell anemia	-	+	-	+	+	ND	NA	NA	NA	NA	NA	NA	NA	Continued improvement	-	
68 (19)†	14y/M	S	Stroke (R hemiparesis)	Sickle cell anemia	-	+	-	+	+	ND	NA	NA	NA	NA	NA	NA	NA	-	-	
69 (51)	7y/M	C	Ischemic stroke (L hemiparesi L-sided paresthesia Central paralysis of the left VII cranial nerve	None	+ (Post NM)	-	-	+	+	+	NA	NA	NA	NA	NA	NA	Acetylsalicylic acid	-	-	
70 (52)	25y/F	C	Ischemic stroke (R hemiparesi Middle cerebral artery thrombosis	None	-	-	-	+	+	+	ND	ND	+	N	N	N	NS	-	-	
71 (53)	33y/F	C	Transverse myelitis	None	+ (With NM)	NK	-	+	NK	NK	+	NK	NK	↑ (181, mainly Mo	N (30)	NK	Steroid (PDN)	Mild weakness of the legs Hypesthesia on the trunk	-	
72 (54)	28y/F	C	Transverse myelitis	None	+ (Pro NM)	-	+	+	+	+	ND	ND	-	N	N (3,3)	ND	Steroids (MPDN, PDN) NSAIDs	Residual weakness affecting legs Required walking sticks to mobilize	-	
73 (55)	Adult, age not reported/ M	C	Parainfectious myelitis	None	-	-	-	+	+	+	-	-	-	↑ (7, mainly L)	Marginally increased CSF:serum albumin ratio	ND	Spontaneous cure	-	-	
74 (56)	3m/M	S	Recurrent seizures	Hypogamma-globulinemic	-	+	-	-	-	+	ND	ND	-	N	N	N	Anti-epileptics IVIG √	-	-	
75 (19)†	6y/F	S	Seizures	Sickle cell anemia	-	+	-	+	ND	ND	NA	NA	NA	NA	NA	NA	NA	Epilepsy	-	
76 (57)	5y/F	C	Frontal lobe seizures Partial epilepsy	Bilateral uveitis	+ (Pro NM)	-	-	+	+	+	NA	NA	NA	3 (93% L,7% Mo)	20	58	Anti-epileptics	-	-	
77 (58)	10m/M	C	Tonic/clonic seizures	Hepatosplenomegaly	+ (Post NM)	+	-	ND	ND	+	ND	ND	+	N	ND	ND	Antibiotics	Persistent hepatosplenomegaly	-	
78 (59)	5y/F	C	Hemiconvulsion-Hemiplegia- Epilepsy Syndrome	History of delayed motor and mental development and cerebellar ataxia from infancy	+ (Pro NM)	-	-		+	+				N	N	N	Midazolam carbamazepine clobazam	Right hemiparesis and mild dysarthria	-	
79 (60)	61y/M	S	Reye's syndrome	Diabetes	-	-	-	+	+	-	NA	NA	NA	N (3)	N	N	Antibiotics	-	+	

NM= neurological manifestations, y= years, m= months, d= days, M= male, F= female, C = competent, S = suppressed, Ne = neutrophils, L = lymphocytes, Mo = monocytes, N = normal, ND= Not done, NA= Not available, NS = not specific, DXM = dexamethasone, MPDN = methylprednisolone; PDN, prednisone IVIG, intravenous immunoglobulin; NSAIDs, non-steroidal anti-inflammatory drugs;
∞ Cerebrospinal fluid (CSF) white blood cells count was considered normal if it was ≤4 cells/µl (≤20 cells/µl for neonates). CSF protein concentration was considered normal if it was≤40 mg/dl (≤90 mg/dl for neonates). CSF glucose con centration was considered normal if
it was ≥40 mg/dl (≥50 mg/dl for neonates). † Cases were found during a retrospective study or a screening program. ¥ Treatment is only mentioned when targeting the neurological symptoms. √ Possible effective treatment.
€ B19 DNA was detected in brain biopsy of patient
No. 13 but of not patient No.25. * Necropsy examination showed neurological dysmorphic features. # The infant's mother had low grade fever, joint pains, a rash on all four limbs and headache. Both the infant and the mother had close contact with the infant's 5 year old
brother, who had EI 17 days previously.

Table 2. Cases of B19 infection and manifestations related to the peripheral nervous system

Case No. (Ref)	Age / Sex	Immune status	Neurological disorders	Other associated disorders	B19 related symptoms			B19 markers in serum			B19 markers in CSF			Other CSF tests∞			Treatment¥	Outcome	
					Rash	Anaemia	Arthralgia	IgM	IgG	DNA	IgM	IgG	DNA	White blood Cells count	Protein (mg/dl)	Glucose (mg/dl)		Neurological sequelae	Death
80 (61)	26y/M	C	Neuralgic amyotrophy	None	+ (With NM)	-	+	+	+	ND	NA	NA	NA	NA	NA	NA	NA	-	-
81(62)	23y/F	C	Neuralgic amyotrophy	None	+ (Pro-NM)	-	+	+	+	ND	NA	NA	NA	N	N	NA	NA	Severe muscle wasting	-
82 (63)	23y/?	C	Neuralgic amyotrophy	None	+ (Pro-NM)		+	+	+	ND	NA	NA	NA	NA	NA	NA	NS	-	-
83 (64)	38y/F	C	Neuralgic amyotrophy	None	+ (With NM)		+	+	+	ND	NA	NA	NA	NA	NA	NA	Steroid √ (MDPN)	-	-
84 (65)	23y/M	C	Neuralgic amyotrophy	None	+ (Pro-NM)			+	+	+	ND	ND	ND	23 (100%M)	50	NA	NSAIDs Antiviral Amitryptiline	Muscle atrophy Dysesthesias	-
85 (66)	33y/F	S	Neuralgic amyotrophy	Crohn's disease	+ (With NM)		+	+	+	-	NA	NA	NA	N	N	NA	Steroid √ (PDN)	Muscle wasting Severely disabled by bilateral symmetrical polyarthritis	-
86 (67)	9y/F	C	Neuralgic amyotrophy	None	-	-	-	+	+	+	NA	NA	NA	NA	NA	NA	Physiotherapy	-	-
87 (68)	23y/M	C	Neuralgic amyotrophy	None	-	-	-	+	+	ND	ND	ND	ND	N	N	N	Steroids Physiotherapy	-	-
88-93 (69)	6 cases F Nurses	C	Paraesthesia	None	+ (4 of them) + (2 of them)	-		+ (All)	+ (All)		NA	NA	NA	NA	NA	NA	NSAIDs	-	-
94 (69-70)	20-40y /F	C	Paraesthesia	None	+ (With NM)	-		+	+	+	NA	NA	NA	NA	NA	NA	NSAIDs	Recurrent episodes of paraesthesia for 4 years	-
95 (71)	37y/F	C	Dysesthesias	None	-	-	-	+	+	+	ND	ND	ND	N	N	N	NA	-	-
96 (72)	57y/F	C	Trigeminal neuralgia Numbness of the right foot in the distribution of the superficial peroneal nerve	Polyarteritis nodosa	+ (With NM)	-	+	+	+	ND	NA	NA	NA	NA	NA	NA	Steroid √ (PDN)	-	-
97 (73)	33y/F	C	Paresthesias along the median nerves and right peroneal nerve	Palpable purpura Polyarteritis nodosa	-	-	+	+	+	+	NA	NA	NA	NA	NA	NA	IVIG √	-	-
98 (74)	16y/M	C	Mononeuritis multiplex	Papular purpuric gloves and socks syndrome	+ (Pro-NM)	-	+	+	-	ND	NA	NA	NA	N	N	NA	IVIG √ Steroids Gabapentin Amitriptyline	-	-
99 (75)	39y/M	C	Sensory motor axonal mononeuropathy multiplex	None	+ (With NM)	-	+	+	+	+	NA	NA	NA	N	N	N	Steroid (PDN) √ IVIG √	Persistent very mild weak- and numbness in both har	
100 (75)	50y/M	C	Pure sensory axonal mononeuropathy multiplex	None	+ (With NM)	-	+	+	+	+	NA	NA	NA	NA	NA	NA	IVIG √	Persistent mild numbness- numbness in L hand and I foot	
101 (75)	40y/F	C	Sensory motor axonal mononeuropathy multiplex	None	-	-	+	+	+	+	NA	NA	NA	N	N	N	Steroid (PDN) √ IVIG √	Severe sensory deficit and motor weakness persi in L hand	-
102 (76)	9y/F	C	Acute autonomic sensory and motor neuropathy	None	+ (Pro-NM)	-	-	+	ND	ND	NA	NA	NA	N	189	ND	IVIG	Persistent dysautonomia	-
103 (77)	1y/M	C	Peripheral facial palsy Cranial nerve VII palsy	Mononucleosis-like syndrome Parotitis	+ (Post NM)	-	-	+	+	ND	NA	NA	NA	N	N	N	NA	-	-
104 (78)	8y/M	C	Unilateral velopalatine paralysis Cranial nerve X palsy	None	-	-	-	+	+	+	NA	NA	ND	NA	NA	NA	Spontaneous cure	-	-
105(79)	39y/F	C	Unilateral optic neuropathy	None	+ (Pro-NM)	-	+	+	+	ND	NA	NA	NA	NA	NA	NA	Steroids √	-	-
106 (80)	40y/M	C	Ophthalmoparesis Cranial nerve VI palsy	None	-	-	-	+	+	+	+	+	+	NA	NA	NA	NK	NK	NK
107 (81)	49y/F	C	Bilateral carpal tunnel syndrome	None	-	-	+	+	+	+	NA	NA	NA	NA	NA	NA	Topical steroids	-	-
108 (81)	38y/F	C	Bilateral carpal tunnel syndrome	None	- #	-	+	+	+	-	NA	NA	NA	NA	NA	NA	NA	-	-
109 (81)	49y/F	C	Bilateral carpal tunnel syndrome	None	+ (With NM)	-		+	+	-	NA	NA	NA	NA	NA	NA	NA	Persistent numbness for 2-	
110 (82)	21-55y/F	C	Carpal tunnel syndrome	None	+		+	+	ND	ND	NA	NA	NA	NA	NA	NA	NA	-	-
111 (82)	21-55y/F	C	Carpal tunnel syndrome	None	+		+	+	ND	ND	NA	NA	NA	NA	NA	NA	NA	-	-
112 (82)	21-55y/F	C	Carpal tunnel syndrome	None	+		+	+	ND	ND	NA	NA	NA	NA	NA	NA	NA	-	-
113 (83)	44y/F	C	Carpal tunnel syndrome	None	+ (With NM)		+	+	+	-	NA	NA	NA	NA	NA	NA		NA	NA
114 (83)	40y/F	C	Carpal tunnel syndrome Myalgic encephalomyelitis Follow-up interval 7m	None	+ (With NM)		+	+	+	+	NA	NA	NA	NA	NA	NA	NA	-	-
115 (84)	42y/F	C	Carpal tunnel syndrome	None	+ (With NM)		+	+	+	+	NA	NA	NA	NA	NA	NA	Surgery	-	-
116 (85)	39y/F	C	Carpal tunnel syndrome	None	- #	-	+	+			NA	NA	NA	NA	NA	NA	Spontaneous	-	-
117 (86)	4y/M	C	Guillain–Barre´ syndrome		+ (Pro NM)	-	-	+	+	+	ND	ND	-	N (4)	↑ (67)	ND	Vitamin B6	-	-
118 (87)	33y/F	C	Guillain–Barre´ syndrome		+ (With NM)	-	-	+	+	+	NA	NA	NA	NA	NA	NA	Double filtrated plasma pheresis	-	-
119 (88)	36y/M	C	Regional Guillain–Barre´ syndrome variant ''facial diplegia and paraesthesias''		-	-	-	+	+	+	ND	ND	+	ND	↑ (68)	ND	IVIG √	-	-
120 (89)	63y/M	S	Guillain–Barre´ syndrome	HIV	-	+	-	-	-	+	-	-	+	N (0)	↑ (60)	ND	IVIG √	-	-

NM= neurological manifestations, y= years, m= months, d= days, M= male, F= female, C = competent, S = suppressed, Ne = neutrophils, L = lymphocytes, Mo = monocytes, N = normal, ND= Not done, NA= Not available, NS = not specific, DXM = dexamethasone, MPDN = methylprednisolone; PDN, prednisone IVIG, intravenous immunoglobulin; NSAIDs, nonsteroidal anti-inflammatory drugs;
∞ Cerebrospinal fluid (CSF) white blood cells count was considered normal if it was ≤4 cells/µl (≤20 cells/µl for neonates). CSF protein concentration was considered normal if it was ≤40 mg/dl (≤90 mg/dl for neonates).
CSF glucose concentration was considered normal if it was ≥40 mg/dl (≥50 mg/dl for neonates). ¥ Treatment is only mentioned when targeting the neurological symptoms. √ Possible effective treatment. # Her child had presented earlier with EI rash.

The majority of the cases (34, 68.0%) were immunocompetent and 16 (32.0%) were immunocompromised. Typical EI rash was observed in 15 cases (30.0%), 13 cases among children (33.0%, 95% CI 20.6–49.0%) and two cases among adults (20%, 95% CI 5.7–51.0%). Only one of these (no. 33) had suppressed immunity, as might be expected from the immunopathological nature of the rash. All 17 cases detected during screening programs or retrospective studies (except one) were free from the rash [8,14,16,19]. The timing of neurological symptoms in relation to the rash varied considerably. B19-associated encephalitis presented prior to the appearance of the rash in five cases, contemporaneously with the appearance of the rash in four cases, or following the appearance of the rash in six cases. There were statistically significant differences between patients with competent and suppressed immune status and symptoms of rash ($p = 0.018$); rash was observed by 42.4% of patients with competent immune status, compared with only 6.2% with suppressed immune status.

Table 3. Cases of B19 infection and myalgic encephalomyelitis

Case No. (Ref)	Age$ / Sex	Immune status	Neurological disorders	Other associated disorders	B19 related symptoms			B19 markers in serum at acute infection			B19 markers in serum at follow-up			Treatment¥	Outcome	
					Rash	Anaemia	Arthralgia	IgM	IgG	DNA	IgM	IgG	DNA		Neurological sequelae	Death
121 (90-91)	45y/M	C	Myalgic encephalomyelitis Follow-up interval 51m	None	-	-	+	+	+	+	-	+	-	NA	-	-
122 (90-91)	17y/F	C	Myalgic encephalomyelitis Follow-up interval 65m	None	-	-	+	+	+	+	-	+	+	NA	-	-
123 (92)	18y/F	C	Myalgic encephalomyelitis Follow-up interval 10m	None	+ (With NM)	-	+	+	+	ND	+	+	+	IVIG √	-	-
124 (83)	42y/F	C	Myalgic encephalomyelitis Follow-up interval 19m	Raynaud syndrome	+ (With NM)	-	+	ND	+	+	ND	ND	+	IVIG √	-	-
125 (83)	34y/F	C	Myalgic encephalomyelitis Follow-up interval 26m	Hyperthyroidism	+ (With NM)	-	+	ND	+	+	ND	ND	+	IVIG √	-	-
126 (83)	46y/M	C	Myalgic encephalomyelitis Follow-up interval 30m	None	-	-	+	ND	-	+	ND	ND	+	IVIG √	-	-
127 (83)	27y/F	C	Myalgic encephalomyelitis Follow-up interval 30m	None	+ (With NM)	-	+	+	+	+	ND	ND	+	NA	-	-
128(93)	39y/F	C	Myalgic encephalomyelitis Follow-up interval 11m	Depression	-	-	-	+	+	+	-	+	+	Anti-depressant	-	-
129 (94)	16y/M	C	Myalgic encephalomyelitis Follow-up interval 24m	None	+ (With NM)	-	-	NK	NK	+	NK	NK	+	IVIG √	-	-

NM= neurological manifestations, y= years, m= months, d= days, M= male, F= female, C = competent, ND= Not done, NA= Not available, IVIG, intravenous immunoglobulin.
$Age was recorded at onset of manifestations. ¥ Treatment is only mentioned when targeting the neurological symptoms. √ Possible effective treatment.

Anemia was detected in 21 cases (42.0%), 17 cases among children (43.6%, 95% CI 29.3–59.0%) and four cases among adults (40.0%, 95% CI 16.8–68.7). There were statistically significant differences between patients with competent and suppressed immune status and symptoms of anemia ($p = 0.002$). The majority of the cases with anemia were observed at reduced immune status (12/16, 75%) comparing with the immunocompetent group (9/34, 26.5%).

Arthralgia was present only in three cases among children (7.7%, 95% CI 2.7–20.3%) and one case among adults (10.0%, 95% CI 1.8–40.4). There were no statistically significant differences between patients with competent and suppressed immune status and symptoms of arthralgia ($p = 0.289$).

Neuroimaging studies (Table 4) were performed on 34 cases using computed axial tomography (20 cases), electroencephalogram (20 cases), and/or magnetic resonance imaging (27 cases). Among

Table 4. Neuroimaging studies for B19-associated encephalitis, encephalopathy and meningoencephalitis cases

Case No. (Ref) †	Computed axial tomography (CAT scan)	Electroencephalogram (EEG)	Magnetic Resonance Imaging (MRI)
5 (9,10)	Normal	ND	Normal
14 (16)	NA	Normal	High signal intensity from the white matter; however, this was thought to be normal for the patient age
15 (16)	ND	Encephalopathic	Wide subarachnoid spaces, enlarged ventricles, and an increased signal from white matter in both T1 and T2 weighted scans
16 (16)	Normal	Encephalopathic	NA
17 (16)	NA	Complete absence of activity	NA
18 (16)	ND	Generalized non-specific activity consistent with encephalitis	Grossly enlarged ventricles, small focal abnormalities in the right frontal white matter, focal abnormalities in the Virchow–Robin spaces, and increased signal from the white matter which was particularly prominent in the parietal lobes in both T1 and T2 weighted scans
20 (16)	Normal	Slowing on the left	Normal
21 (16)	Enlarged ventricles	Encephalopathic	NA
24 (17)	NA	NA	Bilateral symmetric high-signal changes in pulvinar
25 (18)	Normal	Diffuse slowing	Normal
26 (19)	Lesion at right parietal area	NA	NA
27 (19)	Lesion at right parietal area	NA	NA
28 (19)	Lesion at right parietal and occipital areas	NA	NA
29 (19)	Normal	NA	Normal
30 (20)	Normal	NA	Normal
31 (21)	ND	Diffuse slowing, moderate amplitude theta and delta waves, clinically correlating with encephalopathy	Multiple punctate areas of enhancement in the basal ganglia, periventricular white matter, and along the posterior parietal cortex predominantly on the right. The circle of Willis magnetic resonance angiography was normal At 2 weeks: Development of punctate haemorrhages in the previous areas of perivascular enhancement. The distribution (deep grey matter as well as cortex) and configuration (enhancing punctate lesions together with subsequent development of punctate haemorrhage in those areas) were most consistent with a vasculitic process
32(22)	Two small focal areas of cortical enhancement in the right postcentral and middle frontal gyrus	NA	Multiple foci of increased signal intensity involving both cortical and white matter regions of the right frontal lobe without surrounding edema After 4 month: Progression of the brain lesions
33 (23)	NA	At 3 months: Normal At 9 months: Right temporal sharp waves. At 13 months: Diffuse paroxysmal activity. At 40 months: Normal	Up to 6 months: Normal At 13 month: Focal signal flair on right parietal superficial white matter At 15 month: Hyperintense patchy lesions in the cortex and sub-cortical white matter of the right occipital lobe. Magnetic Resonance Angiography (MRA): Severe stenoses in the cavernous segment of both internal carotid arteries and M1 segment of both middle cerebral arteries. At 40 month: The resulting cortical lesion and improvement in vasculitic lesions. MRA: Regression of stenosis of intracranial arteries
34 (24)	Normal	Diffuse slowing and ileptic abnormality in the left hemisphere After 13 days: Frequent electrographic seizure activity from the temporooccipital region of the left hemisphere	Normal
35 (25)	NA	Mild excess slow activity consistent with an encephalopathy, with no change characteristic of herpes simplex encephalitis and no evidence of epileptiform activity	Normal
36 (26)	NA	NA	Extensive contrast enhancement in the frontal and parietal right lobes and in the infratentorial region, consistent with the diagnosis of encephalitis After 4 months: No cerebral sequelae, consistent with the good clinical outcome
37 (27)	10-mm left frontal lobe contusion	Non-specific encephalopathy	NA
38 (28)	Normal	NA	Diffuse hyperintense signals of the white matter: bilateral and symmetric lesions involving the brain stem, the internal temporal lobes, basal ganglia and thalami. After 8 days: Normal.
40 (30)	Abnormalities (Not specified)	Abnormalities (Not specified)	High-intensity signal of periventricular white matter and 2 punctuate areas of enhancement in the corpus callosum in both T1- and T2-weighted scans.
41 (31)	NA	Excess slow activity predominantly on the bilateral frontal and occipital cortex consistent with encephalopathy	Swelling and enhancement in the splenium of the corpus callosum on T2 images
42 (32)	NA	NA	An area in the posterior of the pons-mesen-cephalic region near the cerebral aqueduct and upper part of the fourth ventricle that had an increased signal intensity on both fluid-attenuated inversion-recovery MRI and T2-weighted MR sequence and a decrease in the T1-weighted MR sequence. The altered signal area had a slight mass effect and an irregular but intense contrast gadolinium– diethylenetriamine pentacetic acid enhancement. This irregular and intense impregnation was more evident in the outer part of the lesion, and a necrosis in the initial stages of development was present within it. After 4 weeks: Amelioration of the cerebral lesions. Follow up: Normal.
43 (33)	NA	Generalized slow (theta)- wave activity	Minimal cortical atrophy and gliosis
44 (34)	NA	NA	Subtle cortical increased signal in the left parieto-occipital lobe
45 (35)	NA	NA	Normal
46 (36)	Normal	Normal	Normal
47 (36)	Normal	Normal	Normal
48(37)	Frontal and occipital vasogenic swelling compatible with hypertensive encephalopathy	NA	At admission: bilateral subcortical abnormal signal on the T2 Fluid Attenuated Inversion Recovery (FLAIR) sequence in the fronto-parieto-occipital regions, but no signs of vasculitis or thrombosis. 2 months follow up: Normal.
49 (38)	Normal	Focal slowing with some spikes in front of the left centro-temporo-occipital areas	Normal
50 (39)	Normal	High-voltage delta activity in the bilateral occipital regions, leading to the diagnosis of encephalopathy	Day 6: Marked hyperintensity in the bilateral dentate nuclei in the cerebellum, suggesting a diagnosis of acute cerebellitis. 6 months follow up: Cerebellar atrophy.

ND= Not done, NA= Not available. † Only cases which was examined by one of the tests were included

the computed axial tomography cases, 12 were normal whereas eight showed a range of abnormalities including enlarged ventricles, lesions, frontal, and occipital vasogenic swelling. By electroencephalogram, only three cases were normal whereas 17 showed abnormal activities. Using magnetic resonance imaging, 11 cases were normal whereas 16 showed various abnormalities including enlarged ventricles and increased signal from the white matter. Two cases were normal with all three types of neuroimaging studies.

Excluding 25 cases in which treatment regimen was not known (12 cases), not specific (10 cases), or the encephalitis presentation resolved spontaneously without medical intervention (three cases), most cases were initially treated with antivirals (11 cases) and/or antibiotics (eight cases) to cover a possibility of unidentified viral and/or bacterial encephalitis, respectively, accompanied sometimes with an addition of antiepileptics (10 cases) to relieve the symptoms. However, when B19 involvement was either suspected or confirmed, 16 cases were treated with intravenous immunoglobulins (IVIGs) and/or steroids. Four cases were treated only with IVIG, two of them showing concomitant clinical improvement. Four other cases were treated only with steroids, two of them showing associated clinical improvement. Eight cases were treated with IVIG and steroids (according to the physicians reports about these cases, two showed improvement most probably due to IVIG, two showed improvement most probably due to steroid treatment, while three showed improvement due to combined IVIG and steroids treatment). None of the cases treated with IVIG and/or steroids died but four of them (no. 24, 32, 37, and 50) treated in later stage with either IVIG or steroids (but not both) had mild neurological sequelae. It should be noted that two of these cases had underlying immunodeficiency (no. 24 and 32) while the other two were treated with IVIG alone (no. 50) or steroids alone (no. 37). In contrast, seven out of nine patients who did not receive IVIG and/or steroids were either slow in their recovery (three cases), had a form of neurological sequelae (three cases), or even died (one case). There were no statistically significant differences between patients with competent and suppressed immune status and the success of the treatment (IVIG and/or steroids) ($p = 0.188$).

The prognosis of the encephalitis associated with B19 appears to vary. Although in some cases, complete recovery without neurological sequelae was achieved, there were seven deaths (14.0%) following the illness, and in 13 cases (26.0%), long-term neurological sequelae were observed, ranging from mild language learning difficulties and slurred speech to mental and motor retardation.

DISCUSSION

This is the first systematic review that targets the association between B19 infection and neurological aspects. We identified in this review 129 cases, reported in 89 publications including case reports, brief communications, comments or letters to the editors, retrospective studies or screening programs, and follow-up studies. These publications linked the virus with various neurological aspects either confined to CNS (including encephalitis; 50 cases, meningitis; 12 cases (no. 51–62), cerebellar ataxia as isolated neurological event; one case p (no. 63), stroke; seven cases (no. 64–70), transverse myelitis; three cases (no. 71–73), seizures; five cases (no. 74–78), Reye's syndrome; one case (no. 79)) or related to PNS (including neuralgic amyotrophy; eight cases (no. 80–87), peripheral neuropathy; 19 cases (no. 88–106), carpal tunnel syndrome (CTS); 10 cases (no. 107–116), Guillain–Barré syndrome (GBS); four cases (no. 117–120)), in addition to nine cases that reported an association between B19 infection and ME (no. 121–129).

The most common B19-associated neurological manifestation was encephalitic syndromes, representing 38.8% of the total B19-related neurological cases that are currently in the literature. B19 is not usually investigated during encephalitis episodes, and in most of the cases reported, it was only sought after other pathogens that are commonly involved in encephalitis were proved to be negative, and the etiological cause remained undetermined. In addition, in other cases, B19 was suspected because of the appearance of one of its related symptoms or merely because of the physician anticipation of or interest in B19 infection. This could explain to some extent the rarity of B19 involvement in such a widespread neurological disorder, which occurs at a rate of six to seven cases among 100 000 individuals worldwide [95]. That means if B19 is investigated at the same rate as other pathogens that commonly cause encephalitis, more cases could be detected.

This is supported by the fact that when B19 was sought retrospectively in encephalitis cases, a 4% detection rate was found in the two retrospective studies performed so far, detecting 12 cases with etiologically undiagnosed encephalitis and with no sufficient information to support the detection of a recent B19 infection [14,16]. Therefore, we suggest performing larger multicenter retrospective studies and further prospective studies to support these findings. Because the cost of detecting anti-B19 IgM antibodies and B19 DNA in serum or CSF is relatively low, we recommend at this stage that detection of B19 should be incorporated in the differential diagnosis of encephalitis cases.

The represented cases of B19-associated encephalopathy clearly indicate that there are no distinguishing features of B19-associated encephalitis compared with encephalitis caused by many other viral pathogens, except for the presence of rash, anemia, and arthritis in some patients. It is clear from the evidence of B19 infection upon retrospective analyses that there are no clinical clues regarding the diagnosis [14,16]. For example, physicians cannot depend only on typical EI rash to confirm the concurrent B19 infection with encephalitis because many case reports, especially those identified retrospectively, failed to identify the coexistence of the rash with the encephalitic episode. In addition, the timing of neurological symptoms in relation to the rash varied considerably without a clear pattern. Furthermore, in immunocompromised individuals, B19-specific rash is usually absent around the time of neurological illness because of the immunopathological nature of the rash. Also, a physician cannot depend on the appearance of other B19-related symptoms, such as arthralgia, which is present in few cases, and anemia, which is detected mostly in cases with reduced immune status because of various conditions other than neurological symptoms. On the other hand, analysis of CSF for cell count and protein and glucose concentrations vary among cases, and significant indications cannot be obtained from these data and thus cannot be used in supporting the association of B19 infection in such cases. In addition, physicians cannot rely on neuroimaging studies in detecting specific abnormalities related to B19-associated encephalitis. Therefore, we conclude that the detection or confirmation of associated B19 infection with encephalopathy should always depend on the presence of B19 specific markers, namely, the anti-B19 IgM antibodies and B19 DNA in serum or CSF. However, B19 DNA may be detectable for extended periods, even in healthy individuals [96]. Therefore, the presence of low levels of B19 DNA alone cannot be used to diagnose B19 infection with encephalopathy.

Intravenous immunoglobulin are considered the only treatment option for many clinical syndromes associated with B19 infection because it is believed that they include a good source of antibodies to neutralize the virus, although the mechanism of IVIG action is not precisely known. On the other hand, steroid therapy was also suggested for treatment of neurological disorders in general and encephalopathy in particular. When B19 involvement was either suspected or confirmed, 16 cases of encephalopathy were treated with IVIG and/or steroids. Given the clinical cases of encephalopathy presented, we are clearly not in a position to fully support the use of IVIG, steroids, or their combination in encephalitis associated with B19 infection, although 12 cases showed clinical improvement, because favorable outcomes with full recovery seem to be another distinctive feature for many encephalopathy reported cases without IVIG and/or steroids treatment, which may suggest a casual association with IVIG and/or steroids when they are used. In addition, IVIG and steroids were given together in eight cases showing clinical improvement, and therefore, an objective assessment of efficacy of either treatment cannot be obtained. However, with the absence of other effective treatment regimens, the use of combined treatment of IVIG and steroids in B19-associated encephalopathy could be considered. We, therefore, recommend that treatment of severe cases might benefit from a combined regime of IVIG and steroids, until a randomized prospective clinical trial of this regimen can be conducted.

There were seven deaths following encephalitis associated with B19, and in 12 cases, long-term neurological sequelae were observed, urging the necessity of rapid diagnosis of B19 infection and swift clinical intervention with combined IVIG and steroids regimen. In contrast to encephalitis cases, prognosis appears to be good in cases of B19-associated meningitis with a high rate of spontaneous cure and no sequelae reported.

In addition to one case of ataxia as an individual isolated event in association with B19 [50], there are also six cases where cerebellar involvement was additionally suggested either clinically (no. 16, 20, 44, and 50) or pathologically (no. 17 and 60).

Although aplastic crisis can be, by itself, a risk factor for stroke, B19 could participate in the latter in patients without aplastic crisis. Isolated events of seizures were also reported, although episodes of seizures seemed more part of a wider neurological picture. Scattered case reports have linked B19 infection with transverse myelitis and Reye's syndrome. We are not in a position to confirm these associations because of the low number of cases reported in the literature. Large-scale retrospective studies are required to confirm the association of B19 infection with these CNS presentations.

B19 is generally not regarded to be neurotropic, but direct infection and local replication of the virus could not be ruled out as possible pathogenesis mechanism for B19-associated CNS aspects. There have been controversial reports regarding the detection of B19 DNA in brain tissues. In one study, no evidence of B19 invasion of the brain was observed using relatively insensitive techniques [97]. However, in other reports, B19 DNA was detected in a brain biopsy specimen from a 67-year-old woman with severe meningoencephalitis by PCR [15] and in the nucleus of the multinucleated giant cells and solitary endothelial cells for a hydropic fetus by *in situ* PCR [98]. These data were supported by recent large-scale studies that used a highly specific nested PCR and nucleotide sequencing to detect B19 sequences in the dorsolateral prefrontal cortex [99] and cerebellum [100] of postmortem adult human brains. However, concerns should be cast over the fact that B19 DNA could persist in many tissues in detectable levels for years. In these cases, B19 DNA is likely to be existing in the circulation at high levels after infections and which becomes sequested and persists in the tissues as a result. Distinguishing that remnant DNA from the products of an active infection in a tissue has plagued many studies of B19 pathogenesis. B19 DNA persistence in brain tissues, however, could by itself provoke the pathogenic action of the virus through inducing chromosomal defect or damage [2]. On the other hand, immune-related pathogenic mechanisms cannot be ruled out, supported by complete resolution of symptoms in cases treated with steroids. In addition, recent reports suggest that some cases of anti-*N*-methyl-D-aspartate receptor encephalitis could be triggered by B19 [35,36,101]. Vascular injury, particularly in the cerebellum, could also be involved in the pathogenesis. Therefore, we conclude that complex and variable pathogenesis is likely to contribute to the CNS manifestations. Exact mechanisms of actions through thorough prospective and retrospective pathological studies on sera, CSF, and postmortem tissues are required.

The number of B19-associated neuralgic amyotrophy cases does not necessarily reflect the extent of B19 involvement in this neurological disorder of unknown etiology because all were case reports. Therefore, retrospective and prospective studies are required to give a more comprehensive picture of the involvement of B19 in this disorder. The pathological mechanism of brachial plexus neuritis after B19 infection is also not known. However, clinical characteristics of reported cases show some striking similarities: All cases but one concerned adults, whereas the majority of parvovirus infections usually occur in children. All patients but one presented symptoms of brachial plexus neuritis coinciding with or immediately after the appearance of EI rash, which is interesting because the typical rash is believed to be immune mediated and generally coincides with the appearance of viral antibodies. It is likely that either autoantibodies or immune complex deposition are involved in these cases while direct infection and local replication of the virus could be ruled out.

Reported B19-associated peripheral neuropathy cases occurred as paraesthesia, dysesthesia, cranial nerve palsy, optic neuropathy, mononeuritis multiplex (MM), or acute autonomic sensory and motor neuropathy (AASM). In general, these cases followed a subacute but progressive course with unpredictable extension and severity ranging from complete recovery with no further neurological symptoms to pure limited sensory disorders and could end with severe multifocal sensory motor axonal loss with marked functional disability. The way in which B19 is able to trigger neuropathy is not fully elucidated. Possible mechanisms may involve necrotizing vasculitis through immune complex deposition or hypersensitivity vasculitis secondary to B19 infection. Persistence of B19 infection may play a role in prolongation of the disorder. When followed up, B19 DNA was present in serum beyond 6 months after onset of neuropathy in at least five cases (no. 94–95 and 99–101). This could provide a rationale for the treatment of such patients with IVIG. However, and as discussed in B19-associated encephalitis cases, its combination with steroids in three patients and the possibility of a spontaneous progressive recovery after acute nerve injury does not allow definite conclusions to be made about the efficacy of IVIG in B19-associated neuropathy. Complete neurological, neurophysiological, and nerve histological

examination of B19-associated neuropathy should be performed. Further epidemiological studies are required to confirm the link between B19 and the neuropathy and to assess the frequency of B19-related neuropathy in comparison with other causes of B19-free neuropathy. However, B19 infection should be routinely considered in the etiological assessment, especially in the event of initial sensory symptoms with concurrent rash, as this could lead to an early appropriate treatment with IVIG.

There are several causes of CTS, but in many cases, the etiology remains unknown. The assumptions that B19 can be the infectious agent that triggers CTS, and that the coexistence of B19 infection and CTS was not causal in the reported cases, require prospective and follow-up studies that compare B19 markers (detection and quantification) between CTS patients and a CTS-free control group, preferably during an epidemic peak of B19 infection. This is because most CTS cases are usually confirmed long time after laboratory detection of B19 acute infection.

B19 is not usually cited as a cause of GBS compared with *Campylobacter jejuni* and cytomegalovirus that constitute the most frequent bacterial and viral triggers [102]. Only four cases linked to B19 infection are reported in the literature, and retrospective studies have yet to prove any association. However, it is worth mentioning that, in a relatively old prospective study, serum samples taken from a group of GBS patients were examined for the presence of a variety of pathogens [103]. Anti-B19 IgM antibodies were detected in four patients (4%) but not in controls. Although this was statistically insignificant, this finding suggests that parvovirus B19 may be an important cause of some cases of GBS. These four cases were not included in this study because of insufficient data concerning them.

Few case reports and follow-up studies have documented an association between acute B19 infection and ME (no. 121–129), whereas others found no association [104,105]. Reasons behind this disparity could be due to various groups promoting different nomenclature, diagnostic criteria, etiologic hypotheses, and treatments for ME, resulting in controversy about many aspects of this disorder. For example, ME is not always classified as a neurological disorder. In addition, although ME may follow acute B19 infection, attribution of a case of ME to B19 infection may be extremely difficult in the absence of serological confirmation of acute infection at fatigue onset. Although the gold standard method of diagnosis is to confirm acute B19 infection through positive anti-B19 IgM antibodies or B19 DNA at the time of onset of fatigue, this would be a rare occurrence, and a more practical method would is needed to detect other B19 markers during the illness. Kerr et al. [106] found out that antibodies against B19 nonstructural protein are associated with chronic and not acute B19 infection and therefore could be used as a marker for B19-assciated ME cases. Because several different infections may be involved in ME, the proportion resulting from any one agent, such as B19, is likely to vary, as evident in various follow-up studies, with regard to sampling strategy, time and place, and its relation to the prevalence of each infection. Two particularly important factors are whether there is an outbreak in progress at a particular location and the selection strategy for the control/comparison groups. These factors should be taken into consideration when attempting to confirm the possible link between B19 and ME. Interestingly, five out of nine patients were improved after IVIG [92,94,107], a matter that should be considered when B19 is suspected or confirmed to be associating with ME cases.

This study has various limitations: Firstly, the literature data on this topic are few and heterogeneous in terms of criteria used for characterization of B19-associated neurological symptoms, in addition to the differences in diagnosis, complementary investigation, treatment, and follow-up of these cases. Therefore, epidemiological data on the incidence of B19-associated neurological aspects cannot be accurately extrapolated. Prospective, structured, multicenter studies would be necessary to determine the real epidemiological scenario of these complications that are currently receiving increasing attention. Furthermore, although there are some hypotheses on the pathogenesis of B19-associated neurological aspects, lack of detailed descriptions of autopsy reports render the pathogenesis not completely understood, and therefore, thorough prospective and retrospective pathological studies on postmortem tissues using sensitive immunocytochemistry and *in situ* hybridization techniques are a priority.

In conclusion, pending answers to the questions raised, we recommend that B19 infection should be included in the differential diagnosis of encephalitic syndrome and some PNS manifestations regardless of the age. We recommend that diagnosis of B19-associated neurological aspect should solely depend on the investigation of anti-B19 IgM antibodies and

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B19 DNA in serum or CSF. We also suggest that severe cases of B19-associated neurological aspects might benefit from a combined regime of IVIGs, and steroids and a randomized controlled trial should be considered.

CONFLICT OF INTEREST

The authors have no competing interest.

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