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Severe Arboviral Neuroinvasive Disease in Patients on Rituximab Therapy: A Review

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Abstract

With increasing use of rituximab and other B-cell depleting monoclonal antibodies for multiple indications, infectious complications are being recognized. We summarize clinical findings of patients on rituximab with arboviral diseases identified through literature review or consultation with the Centers for Disease Control and Prevention. We identified 21 patients on recent rituximab therapy who were diagnosed with an arboviral disease caused by West Nile, tick-borne encephalitis, eastern equine encephalitis, Cache Valley, Jamestown Canyon, and Powassan viruses. All reported patients had neuroinvasive disease. The diagnosis of arboviral infection required molecular testing in 20 (95%) patients. Median illness duration was 36 days (range, 12 days to 1 year), and 15/19 (79%) patients died from their illness. Patients on rituximab with arboviral disease can have a severe or prolonged course with an absence of serologic response. Patients

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

should be counseled about mosquito and tick bite prevention when receiving rituximab and other B-cell depleting therapies.

Keywords

arbovirus; arboviral disease; rituximab; anti-CD20; monoclonal antibodies

With increasing use of rituximab and other B-cell depleting monoclonal antibodies for oncological, rheumatological, and neurological indications, potential infectious complications related to these medications are being recognized [1, 2]. Furthermore, because of the profound B-cell depletion induced by rituximab, the clinical characteristics, diagnostic test performance, and outcomes of patients on rituximab who develop infectious diseases are often atypical [2, 3].

Rituximab is a chimeric anti-CD20 monoclonal antibody approved since the 1990s for the treatment of B-cell lymphomas [4, 5]. It causes death of CD20-positive peripheral B-lymphocytes shortly after administration, with effects lasting up to 6–12 months [4]. The approved indications for rituximab have grown over the past two decades [6], and off-label use for autoimmune and inflammatory neurological diseases has also increased [7, 8]. Infectious complications (eg, primary viral infections such as enteroviruses; reactivation of viruses such as herpes viruses, hepatitis B virus, and JC polyomavirus; *Pneumocystis jiroveci* pneumonia) during rituximab treatment are well documented but are considered uncommon [1, 2, 9, 10]. In addition, a growing number of published reports describe arthropod-borne viral (arboviral) disease in patients on rituximab treatment.

Arboviruses are a diverse group of viruses transmitted to humans primarily by mosquitoes and ticks. West Nile virus is the most common cause of human arboviral disease in North America, with nearly 22 000 disease cases reported in the United States from 2009 to 2018 [11]; other less common arboviruses cause sporadic disease and regional outbreaks. In immunocompetent persons, most arboviral infections are asymptomatic or result in a non-specific febrile illness, but a small proportion cause severe disease, including neuroinvasive disease for certain viruses. Patient risk factors such as older age and immunocompromising conditions can lead to greater risk of neuroinvasive disease [12].

Over the past 2 decades, mosquito- and tick-borne diseases have become a growing public health threat, with increasing incidence of domestic disease in the United States, worldwide epidemics, and emergence and spread of novel pathogens [13]. The rising threat of arboviral diseases along with expanding use of novel immunotherapies for a variety of conditions suggest that clinicians are likely to encounter these diseases in vulnerable populations more frequently. The purpose of this review is to summarize the reported clinical characteristics and diagnostic features of arboviral disease in patients on rituximab therapy to improve recognition, diagnosis, and prevention of these diseases.

METHODS

We conducted a literature search of multiple databases, including Medline (OVID), Embase (OVID), and Cochrane Library as of 1 July 2021, limited to English language publications. The following keywords were used: rituximab, ocrelizumab, anti-CD20, monoclonal antibodies, lymphoma, biologics, arbovirus, arboviral, encephalitis, meningoencephalitis, acute flaccid paralysis, neuroinvasive disease, meningitis, encephalomyelitis, West Nile virus, St. Louis encephalitis virus, Powassan virus, dengue virus, Zika virus, tick-borne encephalitis virus, eastern equine encephalitis virus, Jamestown Canyon virus, La Crosse virus, and Cache Valley virus. We also identified additional cases of arboviral disease in patients recently receiving rituximab through a review of consultations and requests for arboviral diagnostic testing at US Centers for Disease Control and Prevention (CDC) from state health departments and clinicians.

The title and abstract of each citation identified by the search strategy were first reviewed, and full text of potentially relevant papers was reviewed independently by two authors (R.K.K., C.V.G.). We included reports describing arboviral disease in patients who had recently (within the previous 12 months) received rituximab or newer anti-CD20 agents with or without other concurrent or previous immunosuppressive therapy.

The following data, where available, were abstracted: age, sex, country/state of residence, exposure history, date of symptom onset, symptoms, clinical syndrome, start of rituximab therapy and last exposure prior to symptom onset, rituximab indication, use of other immunosuppressive medications, arboviral diagnostic test timing and results, laboratory and imaging findings, and outcome.

This project was determined to be a non-research activity by CDC Human Research Protections Senior Advisor review.

RESULTS

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A total of 657 citations were identified as of 1 July 2021. Seventeen patients receiving rituximab with arboviral disease were identified in 15 publications [14–28]. Four additional cases were identified through consultations with CDC, including 2 that were later published [3, 29] (Supplementary Figure 1). No cases involving newer anti-CD20 therapies were identified. Of the 21 patients, the cause of their illness included West Nile (n=13), tick-borne encephalitis (n=3), eastern equine encephalitis (n=2), Cache Valley (n=1), Jamestown Canyon (n=1), and Powassan (n=1) viruses.

The median age of patients was 58 years (range, 28–70 years), and about half were female (Tables 1 and 2). Illness onset for the 14 patients with available data ranged from June to December with 9 (64%) having symptom onset during June–September. Fourteen patients resided in the United States, 2 in Sweden, and 1 each in Australia, Germany, Israel, Italy, and Turkey (Tables 1 and 2).

For 20 patients whose indication for rituximab therapy was provided, 15 (75%) were being treated for lymphoma or leukemia, 3 (15%) for rheumatoid arthritis, 1 for systemic lupus erythematosus, and 1 for post-transplant rejection (Tables 1 and 2). Duration of rituximab therapy prior to symptom onset ranged from 2 weeks to 3 years, and most patients received other previous or concurrent immunosuppressive therapies in addition to rituximab. There were limited data from 8 reports on the quantitation of peripheral B cells counts. Of these, 5 reported no CD19+ or CD20+ cells, and 3 cases reported counts that were mildly depressed or within normal range.

Illness onset occurred a median of 1 month (range, 4 days–26 weeks) following the last dose of rituximab. The details of clinical signs and symptoms varied substantially between reports, although most patient were reported to present with a febrile illness, followed by development of neurologic signs and symptoms, such as confusion, cognitive impairment, dysarthria, tremors, gait disturbance, hemiparesis, ascending paralysis, progressive dementia, unresponsiveness, or coma. The majority (86%, 18) of patients developed encephalitis or meningoencephalitis, including 2 patients with West Nile virus infection who also had acute flaccid paralysis and 1 with Powassan virus infection who also had orchiepididymitis. Two patients had acute flaccid paralysis as their primary clinical syndrome, and 1 patient was described as having West Nile virus neuroinvasive disease, not otherwise specified (Tables 1 and 2).

Duration of illness ranged from approximately 2 weeks to 12 months. In addition to supportive care, 10 of 16 (63%) patients in this case series for whom treatment was reported received intravenous (IV) immunoglobulin G (IgG) therapy, with or without corticosteroids, and 1 patient received West Nile virus hyperimmune globulin. Fifteen of 19 (79%) patients whose outcome was reported died from complications of their arboviral disease (Tables 1 and 2), including 9 of the 11 patients who received a specific treatment for their illness. For the 4 patients who survived, substantial long-term disabilities were noted, including cognitive and motor dysfunction, depressive symptoms, and dependence on others for activities of daily living.

Assessment and Diagnosis

Cerebrospinal fluid (CSF) analysis demonstrated variable white blood cell counts (median 14 cells/μL; range, 0–530), often with lymphocytic (median 55%; range, 4–93) or mixed predominance, frequently elevated protein (median 84 mg/dL; range, 44–230), and normal glucose levels.

Brain imaging results varied among patients. Several patients had initial magnetic resonance imaging findings that were normal, subtle, or non-specific with later progressive T2/fluid-attenuated inversion recovery signal abnormalities (mostly non-enhancing) primarily located in the basal ganglia, thalamus, midbrain, and/or cerebellum. A few patients had leptomeningeal enhancement.

The time from first symptoms until diagnosis ranged from 3 days to 10 months. Diagnosis of arboviral infection was made by molecular testing in 20 (95%) of 21 patients (Tables 1 and 2). Viral ribonucleic acid (RNA) was detected by reverse-transcription polymerase chain

reaction (RT-PCR) in CSF (n=15 patients), serum and/or blood (n=9), urine (n=1), and/or post-mortem brain tissue (n=4). RNA often remained detectable beyond the first week of illness and was detected several months to 1 year after illness onset in some cases. For 1 patient, Jamestown Canyon viral RNA was initially detected by clinical metagenomic sequencing on a CSF sample collected 9 months after symptom onset. Viral antigen was identified by immunohistochemical staining of brain tissue (n=3) and testicular tissue (n=1). Virus was isolated by culture from 2 patients, 1 from urine and 1 from brain tissue. Of 5 patients who had molecular evidence of arboviral infection in brain autopsy tissue, 4 also had RNA detected in serum and/or CSF; the fifth patient only had serologic testing performed (Table 2).

Nineteen of 20 patients who underwent initial serologic testing for the identified arbovirus had negative results, but one patient had evidence of seroconversion at 6-month follow-up. Specimens with negative serologies were collected 3 days to 10 months after symptom onset (Tables 1 and 2).

DISCUSSION

In this case series, arboviral infections in patients on recent rituximab therapy resulted in severe neuroinvasive disease with high fatality. The disease course was often protracted, with prolonged viral RNA detected in clinical specimens and no or delayed serologic response. Molecular methods are usually needed for diagnosis of arboviral disease in patients on rituximab.

The profound immunosuppression in patients receiving rituximab suggests that they might be at high risk of severe disease [30]. B-cells are initially depleted by rituximab within 2–3 days of infusion, remain at low or undetectable levels for up to 6 months, and can take as long as 12 months to return to normal levels [1, 8, 21]. Experimental data suggest that antibodies and B-cells play a critical role in preventing and limiting early neurological dissemination of West Nile virus [31].

Although the clinical syndromes (eg, encephalitis, acute flaccid paralysis, movement disorders) described here are similar to those in other patients with West Nile and other arboviral neuroinvasive disease [32], patients on rituximab in this series had very high mortality with long-term disabilities among survivors, and some patients had atypical, indolent, and protracted courses. Of the patients identified in this case series, 4 out of every 5 patients died. This is higher than what has been reported for other patients with neuroinvasive arboviral diseases where the case fatality ranges from <1% for La Crosse virus disease to 50% for eastern equine encephalitis [33]. Case fatality for West Nile virus neuroinvasive disease typically ranges from 9–11% [11]. Because of the relatively small number of patients in our series and potential for reporting bias, the patients we identified might not be representative of typical arboviral disease in patients on rituximab. In addition, the relative contribution to risk of other immunosuppressive agents and underlying conditions for which rituximab is being prescribed is unknown. In 1 report, an 81-year-old patient with chronic lymphocytic leukemia and hypogammaglobulinemia who was not on treatment developed fatal West Nile virus encephalitis [34]. Serologic testing for West Nile

virus was negative, although it was performed on a blood sample taken on hospital day 2, which might have been too early to detect an immune response. Diagnosis was eventually made by detection of antigen in brain tissue from autopsy, although no West Nile virus RNA was detected in pre-mortem CSF. Older age (>50 years) is also a known risk factor for neuroinvasive disease and death with West Nile virus infection [30]. In this case series, the median age of patients was 58 years. Further study into the contribution of rituximab dosing, duration, pre- and post-rituximab gamma globulin levels, and other immunosuppressive drugs and underlying conditions to severe disease risk is needed.

Most mosquito-borne diseases in the Northern Hemisphere occur during July–September, although Jamestown Canyon virus disease can occur earlier from transmission by snowmelt mosquitoes [35]. Powassan virus and other tickborne arboviruses tend to occur both earlier and later in the year [33]. However, because some patients on rituximab had slow, protracted courses, the usual vector-borne disease onset seasonality (ie, spring through fall) might not apply to patients on similar immunosuppressive therapies.

The diagnosis of arboviral infection can be delayed in patients on rituximab, particularly when clinical symptoms are atypical. In immunocompetent patients, the diagnosis of neuroinvasive arboviral infections is usually made by serologic testing and the presence of virus-specific immunoglobulin M (IgM) and neutralizing antibodies in serum or CSF; by the time symptoms are present, there is often no detectable RNA [12, 36]. In healthy viremic blood donors, the median time from West Nile virus RNA detection to IgM seroconversion is 3.9 days (95% confidence interval [CI]: 3.4–4.4 days) [37]. In patients who are immunocompromised, the ability to mount a cellular and humoral immune response depends on the mechanism and degree of immunosuppression. In the cohort of patients receiving rituximab with resulting B-cell depletion, most did not generate a detectable antibody response, indicating that molecular testing is needed for diagnosis. Although commercial RT-PCR testing is available for West Nile virus, molecular testing is not readily available for most other arboviruses. Clinicians should contact health departments in their jurisdictions to request molecular testing, which can be performed at state public health, CDC, or other diagnostic reference laboratories. Clinically validated metagenomic next-generation sequencing can also be a useful tool, especially when an uncommon or unsuspected infectious disease is the etiology.

Other clues to the diagnosis of arboviral disease might not be present in patients on rituximab. Although CSF profiles were similar to those of other patients with arboviral neuroinvasive disease, the overall white blood cell counts tended to be lower in patients taking rituximab [32, 38]. The lower cell count is likely related to immunosuppression, and caution should be used in interpreting cell counts in patients taking rituximab who are suspected to have neuroinvasive disease. Similarly, neuroimaging of patients on rituximab might not detect acute abnormalities often seen in other patients [32, 39], as inflammation and associated changes are likely slower to develop.

Although various drugs have been evaluated or empirically used for West Nile virus and other arboviral diseases, there are no treatments proven to be effective, and clinical management is supportive [40]. At least half of the patients in this series received IVIg

therapy, with no appreciable effect on outcome, as most of these patients died despite treatment. There are currently no ongoing trials for treatment of domestically acquired arboviral infections. However, a registry of federally and privately supported domestic and international clinical trials is maintained and updated routinely by the National Institutes of Health (https://www.clinicaltrials.gov/).

Since the initial approval of rituximab for non-Hodgkin B-cell lymphoma in 1997, the use of the drug for both approved and off-label indications has been increasing [41, 42]. In 1 healthcare system, the percentage of patients receiving rituximab for an off-label indication increased from 1.2% in 2009 to 55.6% in 2017, driven largely by treatment of demyelinating neurologic conditions [42]. The availability of less expensive biosimilars could continue to drive more off-label use in the future [43]. Clinicians prescribing rituximab and similar B-cell depleting therapies should be aware of the epidemiology and seasonality of arboviral diseases and inform patients of the need to use personal protective measures to prevent vector exposures in areas where they reside and during travel to other endemic areas. Information on local arboviral disease activity can be found on state and local health department and CDC websites (https://wwwn.cdc.gov/arbonet/Maps/ADB_Diseases_Map/index.html). As demonstrated in this review, patients on rituximab may be impacted by domestic and international arboviruses, and an awareness of the global distribution and risk of arboviral diseases is important.

CONCLUSION

In patients taking rituximab, arboviral infections can cause an atypical, severe, and prolonged course of disease often with fatal outcome. Serologic testing for arboviral infections is often non-diagnostic and molecular methods are needed for diagnosis. Personal protective measures against mosquito and tick bites are important to discuss routinely with patients when prescribing rituximab and other B-cell depleting therapies. Although we did not identify any patients taking newer, related anti-CD20 agents (eg, ocrelizumab, veltuzumab, ublituximab), clinicians should remain vigilant about the potential risk of severe arboviral disease in patient receiving similar B-cell depleting therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Summary of Characteristics of Patients on Rituximab With Arboviral Neuroinvasive Disease, N=21

Characteristic	No.	(%)
Sex		
Female	10	(48)
Male	8	(38)
Unknown	3	(14)
Age category in years		
20–39	2	(10)
40–59	9	(43)
60–79	9	(43)
Unknown	1	(5)
Location of residence		
United States	14	(67)
Europe/Middle East	6	(29)
Australia	1	(5)
Month of symptom onset		
June–September	9	(43)
October–December	5	(24)
Unknown	7	(33)
Underlying condition		
Lymphoma or leukemia	15	(71)
Rheumatoid arthritis	3	(14)
Systemic lupus erythematosus	1	(5)
Organ transplant rejection	1	(5)
Unknown	1	(5)
Arboviral diagnosis		
West Nile virus	13	(62)
Tickborne encephalitis virus	3	(14)
Eastern equine encephalitis virus	2	(10)
Powassan virus	1	(5)
Cache Valley virus	1	(5)
Jamestown Canyon virus	1	(5)
Clinical syndrome		
Encephalitis/meningoencephalitis	18	(86)
Acute flaccid paralysis[a]	4	(19)
Orchiepididymitis[b]	1	(5)
Unknown[c]	1	(5)
Laboratory diagnosis of infection (specific for arbovirus diagnosed)		
Molecular (RNA, antigen, or viral culture)	20	(95)
Not tested	1	...

Characteristic	No.	(%)
Serologic (immunoglobulin M antibodies)[d]	1	(5)
Not tested	1	...
Outcome		
Died	15	(71)
Lived	4	(19)
Unknown	2	(10)

[a] All cases of acute flaccid paralysis were due to West Nile virus infection, two with concurrent encephalitis.

[b] With concurrent encephalitis due to Powassan virus infection.

[c] West Nile virus neuroinvasive disease, not otherwise specified.

[d] One patient with West Nile virus infection had RNA detected in blood during the acute illness and later had immunoglobulin M antibodies detected in cerebrospinal fluid at a 6-month follow-up.

Table 2.

Demographics, Clinical Characteristics, Outcomes, and Arboviral Diagnostic Tests Results of Patients on Rituximab With Arboviral Disease

Age Sex	US State or Country	Indication for Rituximab	Arbovirus	Clinical Syndrome	Month of Onset	Died	Specimen	Molecular Testing and Cell Culture Results[a]	Serologic Testing Results[a]	Specimen Collection From Symptom Onset (Days, Except Where Specified)	Ref
70 F	NY	Lymphoma	WNV	E	Sept	Yes	Whole blood	RNA +		6	[17]
							Whole blood	RNA+, virus+		9	
							CSF	RNA+, virus−	IgM−	11	
							Whole blood	RNA+		17	
							Serum	RNA+	IgM−, IgG−	25	
47 F	OH	Lymphoma	WNV	AFP	Oct	Yes	CSF	RNA+	IgM−, IgG−	5	[20]
							Serum		IgM−, IgG−	NR	
57 F	NV	Lung transplant rejection	WNV	E, AFP	Nov	Yes	Serum		IgM−, IgG−	5	[19]
							CSF	RNA+	IgM−, IgG−	5	
							CSF	RNA+	IgM−, IgG−	15	
							Serum		IgM−, IgG−	15	
							Serum		IgM−, IgG−	16	
57 M	Israel	Lymphoma	WNV	E, AFP[b]	NR	Yes	Blood	RNA+	IgM−, IgG−	HD 3	[16]
							CSF		IgM−, IgG−	NR	
							CSF	RNA−	IgM+, IgG−	6 mo	
							Blood	RNA−		6 mo	
							Urine	RNA−		6 mo	
37 M	New York	Lymphoma	WNV	E	Sept	Yes	CSF	RNA+		HD 3	[21]
							Serum	RNA+	IgM−, IgG−	HD 3	
68 M	New Jersey	Lymphoma	WNV	E	Dec	Yes	CSF	RNA+	IgM−, IgG−	HD 7	[21]
							Serum	RNA+	IgM−, IgG−	HD 7	
49 F	Colorado	RA	WNV	E	NR	Yes	Serum		IgM−, IgG−	NR	[15]
							CSF	RNA+	IgM−, IgG−	3	
60 M	Turkey	Lymphoma	WNV	AFP	Aug	Yes	Serum	RNA+	IgM−, IgG−	HD 5	[14]
							Serum		IgM−, IgG−	HD 9	

Age Sex	US State or Country	Indication for Rituximab	Arbovirus	Clinical Syndrome	Month of Onset	Died	Specimen	Molecular Testing and Cell Culture Results[a]	Serologic Testing Results[a]	Specimen Collection From Symptom Onset (Days, Except Where Specified)	Ref
							Serum		IgM−, IgG+	HD 42	
63 F	Australia	Lymphoma	WNV	E	NR	Yes	Serum		IgM−, IgG−[c]	5	[27]
							Whole blood	RNA−[c]		9	
							Whole blood	RNA−[c]		11	
							Urine	RNA+[c,d], virus+		12	
							CSF	RNA−[c]		14	
NR	Italy	Lymphoma	WNV	ND	NR	NR	Serum		IgM−, IgG−	NR	[26]
							CSF	RNA+		NR	
							Whole blood	RNA+		NR	
54 F	Pennsylvania	Lymphoma	WNV	E[e]	NR	No	CSF	RNA+	IgM−	NR	[22]
59 M	New Jersey	Lymphoma	WNV	E	Nov	NR	CSF	RNA+	IgM−	3	U
62 F	South Dakota	NR	WNV	E	Sept	NR	CSF	RNA+	IgM−	6	U
28 NR	Sweden	SLE	TBEV	E	NR	Yes	Serum		IgM+, IgG+	NR	[18]
69 F	Sweden	RA	TBEV	E	NR	Yes	CSF		IgM−, IgG−	NR	[18]
							Serum		IgM−, IgG+[f]	NR	
							Brain tissue	RNA+		NR	
54 F	Germany	RA	TBEV	E	Sept	No	CSF	RNA+	IgM−, IgG−	HD 4	[25]
							Serum		IgM−, IgG−	HD 4	
							CSF	RNA+		HD 6	
							Urine	RNA−		HD 7	
							Serum		IgM−, IgG−	HD 13	
							CSF	RNA−	IgM−, IgG−	HD 13	
63 F	Massachusetts	Lymphoma	EEEV	E	Sept	Yes	CSF	RNA+	IgM−, IgG−	NR	[23]
							Brain tissue	Antigen+		16	
64 F	Alabama	Lymphoma	EEEV	E	Sept	Yes	CSF	RNA+	IgM−	24	[29]
							Serum	RNA+	IgM−, Neut−	24	
63 M	Massachusetts	Lymphoma	POWV	E[g]	Dec	Yes	CSF	RNA+	IgM−	24	[24]

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Age Sex	US State or Country	Indication for Rituximab	Arbovirus	Clinical Syndrome	Month of Onset	Died	Specimen	Molecular Testing and Cell Culture Results[a]	Serologic Testing Results[a]	Specimen Collection From Symptom Onset (Days, Except Where Specified)	Ref
							Serum	RNA+	IgM−	24	
							Testicular tissue	Antigen+		24	
							Brain tissue	Antigen+, RNA+		24	
58 M	New York	Leukemia	CVV	E	June	Yes	CSF	RNA+		HD ~7	[28]
							Brain tissue	RNA+, antigen +, virus+		3 mo	
56 M	New Hampshire	Lymphoma	JCV	E	July	Yes	CSF	RNA+		9 mo	[3]
							CSF	RNA−	IgM−, Neut−	10 mo	
							Serum	RNA+	IgM−, Neut−	10 mo	
							Brain tissue	RNA+		12 mo	

Abbreviations: AFP, acute flaccid paralysis; CSF, cerebrospinal fluid; CVV, Cache Valley virus; E, encephalitis or meningoencephalitis; EEEV, eastern equine encephalitis virus; F, female; HD, hospital day; Ig, immunoglobulin; JCV, Jamestown Canyon virus; M, male; ND, neuroinvasive disease; Neut, neutralizing antibodies; NR, not reported or unknown; POWV, Powassan virus; RA, rheumatoid arthritis; Ref, reference; RNA, ribonucleic acid; SLE, systemic lupus erythematosus; TBEV, tick-borne encephalitis virus; U, unpublished; WNV, West Nile virus; (+), detected; (−), not detected.

[a] Specific for the arbovirus diagnosed.

[b] Followed by delayed-onset polyneuropathy.

[c] Flavivirus assays.

[d] WNV confirmed by sequencing.

[e] With Parkinsonism.

[f] Patient previously received TBEV vaccination.

[g] And orchiepididymitis.