

# A comprehensive neurological perspective on tick-borne flaviviruses, with emphasis on Powassan virus

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**Abstract:** Powassan virus (POWV), a tick-borne flavivirus transmitted primarily by Ixodes ticks, poses a significant threat as it can lead to severe neuroinvasive illness. This review delves into the nuanced clinical presentation of Powassan infection, a challenge in diagnosis exacerbated by the absence of an available vaccine. Over the past decade, the prevalence of POWV has surged in North America, necessitating a thorough examination of its neurological manifestations alongside tick-borne encephalitis virus (TBEV). A comprehensive literature search conducted up to January 2024 revealed 135 cases of neurological symptoms associated with either Powassan or TBEV infection. Notably, severe occipital headache emerged as the most prevalent symptom (22.75%), followed by meningoencephalitis (10.34%), seizures (8.27%), and flaccid paresis (6.8%). Additional manifestations included poor balance, wide gait, dysarthria, facial nerve palsy, seizure, slurred speech, and absent deep tendon reflexes. Tragically, nine cases resulted in fatal outcomes attributed to POWV infection. This analysis highlights the intricate spectrum of neurological symptoms associated with Powassan infection and underscores the necessity for heightened awareness among medical practitioners, particularly in regions with a higher prevalence of the virus. The complexity of symptoms emphasizes the need for further research to unravel the factors contributing to this diversity. Additionally, exploring potential treatment avenues and vaccine development is crucial in addressing the rising threat posed by POWV, ultimately enhancing our ability to manage and prevent severe neurological outcomes.

**Keywords:** encephalitis, neuroinvasive disease, Powassan virus, tick-borne encephalitis virus, tick-borne flavivirus

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## Introduction

Powassan virus (POWV), belonging to the *Flavivirus* genus, is closely akin to tick-borne encephalitis virus (TBEV), which has been extensively studied in both Europe and Asia, with more than 10,000 cases, posing an increasing threat to public health. In humans, TBEV induces central nervous system (CNS) infections, with the potential for severe consequences, including lasting neurological complications and, in some cases, fatality.<sup>1</sup> Like TBEV, POWV is transmitted by ticks and can inflict significant damage to the nervous system. Its recognition as a human pathogen dates back to 1958, originating from the

isolation of the virus in the brain of a young child who succumbed to encephalitis in Powassan, Ontario.<sup>2,3</sup> The virus is categorized into two distinct lineages: lineage 1 (POWV), found in North America and far Eastern Asia, and lineage 2 (DTV), exclusively present in North America. Despite representing two genotypes of the same virus, these lineages cannot be differentiated through serological methods.<sup>3,4</sup> Ticks from the *Ixodes* genus, including species like *Ixodes cookei* (lineage 1), *Ixodes marxi* (lineage 1), and *Ixodes scapularis*, also known as the black-legged or deer tick (lineage 2), act as the primary carriers of the POWV. Graphical representation of the Powassan

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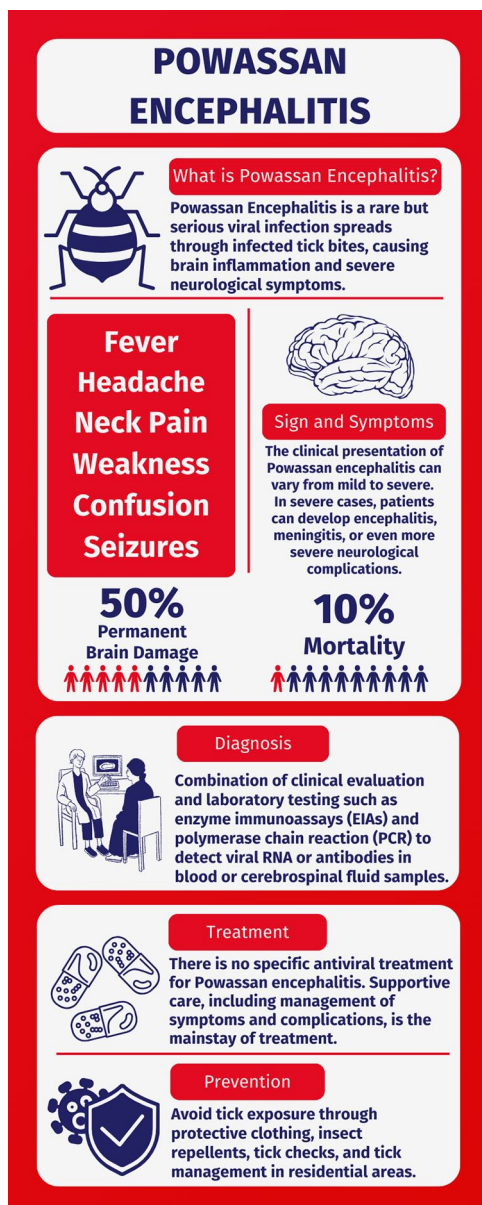
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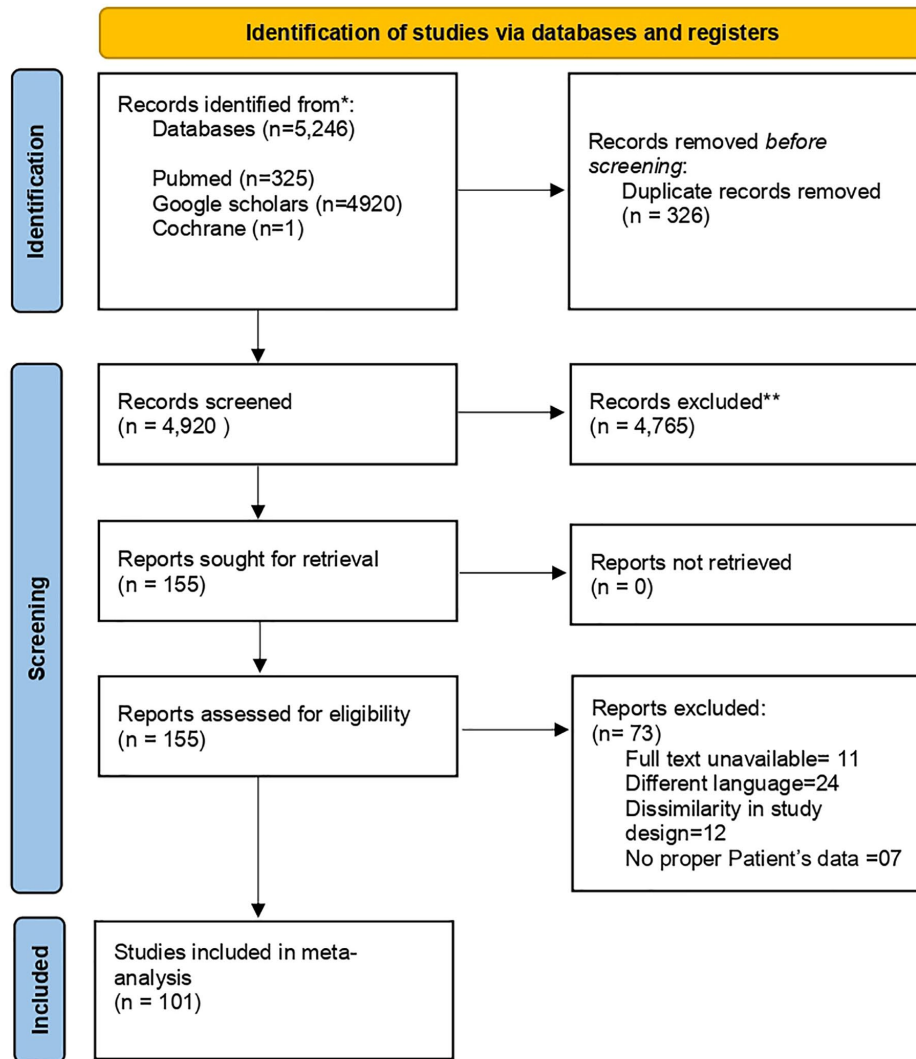
**Figure 1.** Graphical representation of the POWV encephalitis. POWV, Powassan virus.

virus (POWV) Encephalitis is depicted in Figure 1. The virus is transmitted to humans through the bite of an infected tick, which has previously been fed to animals such as groundhogs, squirrels, mice, or other rodents carrying the virus in their bloodstream.<sup>5,6</sup> In addition to the recognized transmission modes, there exist alternative pathways, including trans-stadial transmission, vertical transmission to offspring and transmission through infected milk, through which the POWV

may propagate. Integrating these lesser-explored transmission routes into ongoing research and surveillance endeavors holds the promise of attaining a more holistic comprehension of POWV dynamics.<sup>7,8</sup>

Due to the POWV's diverse clinical presentation and the absence of precise diagnostic techniques that match the intensity and complexity of the disease, this virus is regarded as a diagnostic challenge. The POWV currently lacks a vaccine, thus individuals who are afflicted only get supportive care and symptomatic therapy.<sup>2</sup> While the POWV has historically been infrequent, there has been a notable surge in cases over the past decade in both the United States and Canada. In the United States, the majority of POWV cases have been concentrated in the New England and Great Lakes regions. Specifically, the highest annual case counts are reported in Minnesota, Wisconsin, Massachusetts, and New York.<sup>9</sup> Typically associated with a 10% mortality rate post-infection, survivors often grapple with enduring neurological consequences, affecting at least 50% of those who recover.<sup>4</sup> Despite its relative rarity, POWV cases have been consistently documented each year since the confirmation of the first case in Minnesota in 2008. In 2021, Minnesota reported five instances of Powassan viral disease, all presenting severe neurological conditions – either meningitis or encephalitis – resulting in two fatalities. Individuals afflicted with such extreme cases commonly endure persistent medical issues, including recurrent headaches, loss of muscle strength and mental challenges.<sup>10,11</sup> The prevalence of long-term outcomes is observed in approximately half of individuals with encephalitis or meningitis, with 10–15% of cases ultimately resulting in death.<sup>10</sup>

An imperative demand for in-depth research and analysis on this flavivirus, particularly concerning its neurological manifestations, arises due to the existing gaps in our understanding of the POWV and its neurotropic properties. Conducting a comprehensive study could yield advancements in diagnostic methods, alternative treatments and potentially even the development of a vaccination. Our focus will extend beyond Powassan to include the tick-borne encephalitis (TBE) virus, given the limited availability of studies on Powassan, as we aim to scrutinize the neurological symptoms associated with these viruses.



\*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

\*\*If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

**Figure 2.** PRISMA flowchart.  
PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.

## Methods

### *Data sources and search strategy*

This study followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines<sup>12</sup> shown in Figure 2.

We used MESH phrases and ‘AND’ and ‘OR’ to conduct an organized literature search in

PubMed, Google Scholar, and Cochrane Library. We used the following search terms:

Powassan AND [‘encephalities’ (All Fields) OR ‘encephalitis’ (MeSH Terms) OR ‘encephalitis’ (All Fields)]. Our objective was to encompass studies exploring neurological manifestations akin to those associated with POWV or TBEV, even if not explicitly tied to POWV itself.

### Study selection and eligibility criteria

Without regard to language, we accessed databases from their creation until January 2024. Studies that matched the following PICO's criteria were included in our analysis: (1) Individuals with a medical history featuring neurological manifestations similar to those linked with the POWV, even if not directly connected to Powassan, are included. This encompasses patients discussing symptoms or diseases comparable to those associated with TBEV. (2) Following infection, some individuals had incident encephalitis. (3) Case-reporting and case-series publications that describe the symptoms and (4) articles in English should be evaluated for inclusion. Following studies were excluded: Reports without a prior history of encephalitis or situations when encephalitis had already existed before the infection. (1) Articles in which the authors concluded that a different aetiology may account for encephalitis, (2) case-unspecific studies, and (3) abstracts or articles that were not available as full text.

### Data extraction

Two investigators (SR and UZ) independently extracted the following information from each included study: study characteristics (first author, year of publication, country, sample size, and study type) and participant baseline characteristics. Any disparities among the reviewers were resolved through group discussions, continuing until a consensus was achieved.

### Risk of bias and quality assessment

Two authors (SR and UZ) independently assessed the risk of bias in the included studies using the Murad scale. This evaluation considered six evidence-based criteria, examining aspects such as selection, representativeness of cases, ascertainment of outcomes and exposure, and comprehensive reporting.<sup>13</sup> The questions utilized for the assessment of each study can be found in Supplemental Table S1. The classification of study bias was determined based on the number of criteria met. A study was categorized as having a low risk of bias if all six criteria were met, a moderate risk of bias if five or four criteria were met, and a high risk of bias if three or fewer criteria were met.<sup>14</sup> The corresponding scores for each study can be found in Supplemental Table S1.

Any discrepancy between data extractions was resolved by the discussion or consultation with the third author (AF).

## Results

### Literature search

The study selection process is illustrated in Figure 2, which presents a thorough PRISMA flow-chart.<sup>12</sup> Following the preliminary literature search, a total of 5246 articles were identified. After removing 326 duplicates, 4920 articles underwent screening. Upon screening, 4765 were excluded based on title and abstract review. After the full-text screening of 155 studies, 101 studies<sup>15–115</sup> were deemed appropriate for inclusion in this Review. The main characteristics of the included studies such as demographic data (age and gender), study design, publication year, study location, time of infection, incubation period, and time from onset of symptoms to diagnosis are presented in Tables 1 and 2, respectively.

### Study characteristics

The review comprises an analysis of 101 studies that involve patients discussing symptoms or illnesses related to either the POWV or TBEV across a multitude of countries. These studies comprise a mix of case reports and case series, varying from individual instances to multiple cases within a series. The countries under investigation exhibit a wide-ranging diversity, spanning the USA, Sweden, Croatia, Russia, Germany, Poland, Switzerland, England, Denmark, Belgium, France, Austria, Italy, Netherlands, Finland, Saudi Arabia, Norway, Bulgaria, Turkey, Australia, Ireland and specific regions such as New York and Europe presented in Table 1.

### Quality assessment

Murad scale was employed to evaluate the risk of bias in the included studies.<sup>13</sup> The majority of studies demonstrated either a low or moderate risk of bias represented in Supplemental Table 1.

### Neurological manifestations

The dataset comprises a diverse array of research conducted in various countries, including the USA, Sweden, Croatia, Germany, Poland, and

**Table 1.** Study characteristics of the included studies.

S.No.	Author	Year	Country	Study design	Sample size	Male	Female	Age	Cause of disease	Time of infection	Incubation period
1	Yu <i>et al.</i> <sup>15</sup>	2020	USA	Case report	1	Male		88	POWW	2 weeks	2 weeks
2	Pach <i>et al.</i> <sup>16</sup>	2021	USA	Case report	1	Male		62	POWW	N/A	N/A
3	Khan <i>et al.</i> <sup>17</sup>	2019	USA	Case report	1	Male		87	POWW	28 days	4 days
4	Solomon <i>et al.</i> <sup>18</sup>	2018	USA	Case report	1	Male		63	POWW	14 days	14
5	Bazer <i>et al.</i> <sup>19</sup>	2022	USA	Case report	1	Male		62	POWW	None	7–34 days
6	Dumic <i>et al.</i> <sup>20</sup>	2021	USA	Case report	1	Male		76	POWW	36 days	8 days
7	Eleftheriou <i>et al.</i> <sup>21</sup>	2019	Sweden	Case report	1	Male			TBEV	26 days	10 days
8	Mittal <i>et al.</i> <sup>22</sup>	2017	USA	Case report	1	Male		35	POWW	16 months	1.5 weeks
9	Vilibic-Cavlek <i>et al.</i> <sup>23</sup>	2022	Croatia	Case report	1	Male		Early 20s	TBEV	N/A	5 days
10	Colman <i>et al.</i> <sup>24</sup>	2020	USA	Case report	1	Male		56	POWW	N/A	5 days
11	Dumic <i>et al.</i> <sup>25</sup>	2021	USA	Case report	1	Male		42	POWW	36 days	1 day
12	Kakoullis <i>et al.</i> <sup>26</sup>	2022	USA	Case report	1	Male		75	POWW	34 days	9 days
13	Birge and Sonnesyn <sup>27</sup>	2012	USA	Case report	1		Female	67	POWW	N/A	1 week
14	Tavakoli <i>et al.</i> <sup>28</sup>	2009	USA	Case report	1	Male		62	POWW	17 days	4 days
15	Henningsson <i>et al.</i> <sup>29</sup>	2016	Sweden	Case report	1	Male		67	TBEV	28 days	2 days
16	Voulgari <i>et al.</i> <sup>30</sup>	2021	Switzerland	Case report	1	Male		58	TBEV	3 weeks	8 days
17	Yurchenko <i>et al.</i> <sup>31</sup>	2021	Russia	Case report	1	Male		55	TBEV	N/A	5 days
18	Divé <i>et al.</i> <sup>32</sup>	2020	Germany	Case report	1		Female	30	TBEV	N/A	N/A
19	Czarnowska <i>et al.</i> <sup>33</sup>	2022	Poland	Case report	1		Female	24	TBEV	N/A	N/A
20	Cavanaugh <i>et al.</i> <sup>34</sup>	2017	North America	Case report	1		Female	72	POWW	20 days	10 days
21	Allgaier <i>et al.</i> <sup>35</sup>	2019	USA	Case report	1	Male		55	POWW	2 weeks	1 week
22	Neill <i>et al.</i> <sup>36</sup>	2019	England	Case report	1	Male		38	TBEV	17 days	14 days
23	Weinmayr <i>et al.</i> <sup>37</sup>	2020	Germany	Case report	1		Female	26	TBEV	N/A	N/A
24	Kristiansen <sup>38</sup>	2002	Denmark	Case report	1	Male		41	TBEV	N/A	N/A

*(Continued)*

Table 1. (Continued)

S.No.	Author	Year	Country	Study design	Sample size	Male	Female	Age	Cause of disease	Time of infection	Incubation period
25	Boyer <i>et al.</i> <sup>39</sup>	2017	Western Europe	Case report	1	Male		66	TBEV	21 days	8 day
26	Zachary <i>et al.</i> <sup>40</sup>	Crist		Case report	1		Female	70	POWV	3 weeks	3 days
27	Velay <i>et al.</i> <sup>41</sup>	2023	Germany	Case report	1		Female	34	TBEV	N/A	N/A
28	Lotrič-Furlan <i>et al.</i> <sup>42</sup>	2005	Slovenia	Case report	1		Female	47	TBEV	N/A	N/A
29	Pogorzelski <i>et al.</i> <sup>43</sup>	2006	Poland	Case report	1		Female	39	TBEV	N/A	N/A
30	Cimperman <i>et al.</i> <sup>44</sup>	2002		Case report	1				TBEV	N/A	N/A
31	McNair and Brown <sup>45</sup>	1991	England	Case report	1		Female	44	TBEV	N/A	N/A
32	Gils <i>et al.</i> <sup>46</sup>	2018	Belgium	Case report	1		Female	45	TBEV	2 months	12 days
33	Agergaard <i>et al.</i> <sup>47</sup>	2019	Denmark	Case report	1	Male		N/A	TBEV	N/A	N/A
34	Weststrate <i>et al.</i> <sup>48</sup>	2016	Netherlands	Case report	1	Male		44	TBEV	N/A	N/A
35	Iff <i>et al.</i> <sup>49</sup>	2015	Switzerland	Case report		Male		N/A	TBEV	14 days	N/A
36	Zajkowska <i>et al.</i> <sup>50</sup>	2011	Poland	Case report	1	Male		49	TBEV	10 days	N/A
37	Arnež <i>et al.</i> <sup>51</sup>	2009		Case report	1	Male		N/A	TBEV	N/A	N/A
38	Ananthan <i>et al.</i> <sup>52</sup>	2014	USA	Case report	1	Male		44	POWV	2 weeks	N/A
39	Choi and Taylor <sup>53</sup>	2012	USA	Case report	1	Male		43	POWV	N/A	27 days
40	Zajkowska <i>et al.</i> <sup>54</sup>	2013	Poland	Case report	1	Male		38	TBEV	1 month	N/A
41	Herpe <i>et al.</i> <sup>55</sup>	2007	France	Case report	1	Male		70	TBEV	N/A	N/A
42	Bologheanu <i>et al.</i> <sup>56</sup>	2020	Austria	Case report	1	Male		22	TBEV	14 days	N/A
43	Pessa <i>et al.</i> <sup>57</sup>	2019	Italy	Case report	1		Female	62	TBEV	N/A	N/A
44	de Graaf <i>et al.</i> <sup>58</sup>	2016	Netherlands	Case report	1	Male		60	TBEV	21 days	2 days
45	Lessell and Collins <sup>59</sup>	2003	USA	Case report	1		Female	53	POWV	With in days	13 days
46	Takashima <sup>60</sup>	1998	Japan	Case report	1	Male		N/A	TBEV	2 days	3 days
47	Waldvogel <i>et al.</i> <sup>61</sup>	1996	Switzerland	Case report	1	Female		5	TBEV	2 month earlier	N/A

(Continued)

Table 1. (Continued)

S.No.	Author	Year	Country	Study design	Sample size	Male	Female	Age	Cause of disease	Time of infection	Incubation period
48	Fomsgaard et al. <sup>62</sup>	2009	Denmark	Case report	1	Male		40	TBEV	1 week	2 weeks
49	Tajima et al. <sup>63</sup>	2018	Japan	Case report	1	Male		44	TBEV	N/A	N/A
50	Rácz et al. <sup>64</sup>	2010	Germany	Case report	1	Male		39	TBEV	N/A	N/A
51	Cruciatti et al. <sup>65</sup>	2003	Italy	Case report	3	Male Male	Female	36 N/A N/A	TBEV	1.22 days 2.3 days 3.26 days	1.24 days 2.9 days 3.26 days
52	Enzinger et al. <sup>66</sup>	2009	Austria	Case report	1	Male		58	TBEV	3 weeks	N/A
53	Bender <sup>67</sup>	2003	Germany	Case report	1	Male		29	TBEV	2 days	3 weeks
54	Hemmer et al. <sup>68</sup>	2004	Germany	Case report	1	Male		61	TBEV	9 days	10 days
55	Mázió and Szántó <sup>69</sup>	1976	Hungary	Case report	1	Male		37	TBEV	18 days	20 day
56	Raval et al. <sup>70</sup>	2012	USA	Case series	4	Male		18-69	POWV	N/A	N/A
57	Piantadosi et al. <sup>71</sup>	2016	England	Case series	8	Male=7	Female=1	21-82	POWV	N/A	N/A
58	CDC <sup>72</sup>	1999-2001	USA	Case series	4	Male		25-70	POWV	N/A	N/A
59	Botelho-Nevers et al. <sup>73</sup>	2017	France	Case series	2	Male=1	Female=1	76 66	TBEV	N/A N/A	N/A N/A
60	Ponfick et al. <sup>74</sup>	2011	Germany	Case series	5	Male		21-77	TBEV	N/A	N/A
61	Kuivanen et al. <sup>75</sup>	2015	Finland	Case report	1		Female	36	TBEV	10 days	17 days
62	Sung et al. <sup>76</sup>	2013	USA	Case series	2	Male		22 34	POWV	2 months N/A	2 weeks N/A
63	Zaki <sup>77</sup>	1997	Saudi Arabia	Case series	2	Male		24 39	TBEV	N/A N/A	N/A N/A
64	Skarpaas et al. <sup>78</sup>	1997	Norway	Case series	3	Male		62 53 74	TBEV	N/A N/A 3 days	2 weeks later N/A N/A
65	Mease <sup>79</sup>	2017	Germany	Case report	1	Male		36	TBEV	N/A	N/A
66	Schultze et al. <sup>80</sup>	2004	Switzerland	Case report	1	Male		47	TBEV	4 day	3 week

(Continued)

Table 1. (Continued)

S.No.	Author	Year	Country	Study design	Sample size	Male	Female	Age	Cause of disease	Time of infection	Incubation period
67	Voshii <i>et al.</i> <sup>81</sup>	2018	Japan	Case series	158	N/A	N/A	N/A	TBEV	N/A	N/A
68	Mohareb <i>et al.</i> <sup>82</sup>	2009–2012	Bulgaria	Case series	2	N/A	N/A	N/A	TBEV	N/A	6 days before hospital admission
69	Reuksen <i>et al.</i> <sup>83</sup>	2011	Netherlands	Case series	2	Female	Female	50	TBEV	1 week 16 days	10 days 1 week
70	Koray <i>et al.</i> <sup>84</sup>	2012	Turkey	Case series	13	Male	Male	68	TBEV	N/A	N/A
71	Kleiter <i>et al.</i> <sup>85</sup>	2006		Case series	5	Male	Male	48–71	TBEV	N/A	N/A
72	Chaudhuri and Růžek <sup>86</sup>	2017	Australia	Case report	1	Male	Male	60	TBEV	6 week	N/A
73	Doyle <i>et al.</i> <sup>87</sup>	2022	Ireland	Case report	1	Male	0	50	TBEV	N/A	N/A
74	Nord and Goldberg <sup>88</sup>	2021	New York	Case report	1	Male	0	51	POWV	3 weeks	5 weeks
75	Four <i>et al.</i> <sup>89</sup>	2017	Belgium	Case report	1	Male	1	23	TBEV	N/A	N/A
76	Tanaka <i>et al.</i> <sup>90</sup>	2021	Japan	Case report	1	Male	1	43	TBEV	24 days	N/A
77	Montydaite <i>et al.</i> <sup>91</sup>	2022	Europe	Case report	1	Female	Female	33	TBEV	N/A	N/A
78	Hockicková <i>et al.</i> <sup>92</sup>	2019		Case report	1	Female	Female	N/A	TBEV	N/A	N/A
79	de Bruijn <i>et al.</i> <sup>93</sup>	2015	Germany	Case report	1	Female	Female	48	TBEV	2 weeks	8 days
80	Walder <i>et al.</i> <sup>94</sup>	2001	Austria	Case report	1	Female	Female	55	TBEV	N/A	N/A
81	McLean <i>et al.</i> <sup>95</sup>	1959	Canada	Case report	1	Male	Male	5	POWV	N/A	3 weeks
82	Goldfield <i>et al.</i> <sup>96</sup>	1973	USA	Case report	1	Female	Female	57	POWV	N/A	N/A
83	Smith <i>et al.</i> <sup>97</sup>	1974	USA	Case series	3	Male	Male		POWV	20 days 6 days 6 days	N/A N/A 12 days
84	Rossier <i>et al.</i> <sup>98</sup>	1974	Canada	Case report	1	Male	Male	8	POWV	34 days	6 days
85	Wilson <i>et al.</i> <sup>99</sup>	1979	Canada	Case report	1	Female	Female	13 month	POWV	3 weeks	3 weeks
86	Parington <i>et al.</i> <sup>100</sup>	1980	Canada	Case report	1	Male	Male	7	POWV	N/A	N/A

(Continued)



Table 1. (Continued)

S.No.	Author	Year	Country	Study design	Sample size	Male	Female	Age	Cause of disease	Time of infection	Incubation period
87	Embil <i>et al.</i> <sup>101</sup>	1983	USA	Case report	1	Male			POWV	72 h	9 days
88	Fitch and Artsob <sup>102</sup>	1990	Canada	Case report	1	Male		70	POWV	N/A	N/A
89	Gholam <i>et al.</i> <sup>103</sup>	1999	Canada	Case report	1	Male			POWV	3 days	2 weeks
90	Courtney <i>et al.</i> <sup>104</sup>	2001	USA	Case series	4	Male	Female	70 53 25 66	POWV	N/A	N/A
91	Hinten <i>et al.</i> <sup>105</sup>	2008	USA	Case series	9	Male	Female	70 53 25 74 66 69 60 83 91	POWV	N/A	N/A
92	Trépanier <i>et al.</i> <sup>106</sup>	2010	Canada	Case report	1	Male		61	POWV	3 days	N/A
93	Hicar <i>et al.</i> <sup>107</sup>	2011	USA	Case report	1		Female	9	POWV	3 days	7 days
94	Tutolo <i>et al.</i> <sup>108</sup>	2017	USA	Case report	1	Male		5 month	POWV	N/A	2 weeks
95	Sanderson <i>et al.</i> <sup>109</sup>	2018	Canada	Case report	1		Female	68	POWV	3 weeks	3 weeks
96	Patel <i>et al.</i> <sup>110</sup>	2018	USA	Case report	1		Female	81	POWV	N/A	N/A
97	Picheca <i>et al.</i> <sup>111</sup>	2019	Canada	Case report	1	Male		68	POWV	N/A	N/A
98	Koester <i>et al.</i> <sup>112</sup>	2020	USA	Case report	1		Female	8	POWV	3 days	N/A
99	Taylor <i>et al.</i> <sup>113</sup>	2021	USA	Case report	1		Female	30	POWV	33 days	24 days
100	Kroopnick <i>et al.</i> <sup>114</sup>	2021	USA	Case report	1		Female	82	POWV	1 month	N/A
101	Johnson <i>et al.</i> <sup>115</sup>	2022	USA	Case series	2	Male Male		68 75	POWV	N/A	N/A
POWV, Powassan virus; TBEV, tick-borne encephalitis virus.											

**Table 2.** Summary of symptoms, time from onset of symptoms to diagnosis and overall survival.

S.No.	Author	Cause of disease	Symptoms	Time from onset of symptoms to diagnosis	Survival
1	Yu <i>et al.</i> <sup>15</sup>	POWV	Meningoencephalomyelitis	6–12 months	Death
2	Pach <i>et al.</i> <sup>16</sup>	POWV	Fevers, headaches, and fatigue, malaise	N/A	Overall survival
3	Khan <i>et al.</i> <sup>17</sup>	POWV	Fever: Up to 103°F (39.4°C), rigours and chills, vomiting, drowsiness, worsening, fatigue, malaise, intermittent lightheadedness, mild abdominal pain	2 weeks	Overall survival
4	Solomon <i>et al.</i> <sup>18</sup>	POWV	Testicular pain, fever, dysarthria, gait instability, low-grade fever, meningismus, bilateral upper extremity dysmetria, obtunded, lack of eye opening, absent response to pain, intubation status	7 days	Death on day 14
5	Bazer <i>et al.</i> <sup>19</sup>	POWV	Altered mental status, dysarthria, left facial droop, recurrent stroke, tick bites, acute to subacute left putamen infarct, cerebellar involvement, splenium of corpus callosum involvement, elevated WBCs in CSF, elevated protein in CSF, glucose abnormalities in CSF, axon loss with demyelinating polyradiculopathy, positive Powassan virus markers in CSF	1–3 days	Overall survival
6	Dumic <i>et al.</i> <sup>20</sup>	POWV	Meningoencephalitis	1 day	Overall survival
7	Eleftheriou <i>et al.</i> <sup>21</sup>	TBEV	Fever (up to 38.5°C), malaise and fatigue, temporary improvement followed by worsening, headache, progressive monoparesis in the lower right extremity, paretic right leg with difficulty in walking, hyperreflexia of the right patella, no Babinski's sign, slight thrombocytopenia, lymphopenia, elevated transaminases	33 days	Overall survival
8	Mittal <i>et al.</i> <sup>22</sup>	POWV	Headache, vomiting, confusion, hypertension, fever. Rightward gaze deviation, poor respiratory function requiring ventilation, minimally responsive after sedation withdrawal, reduced short-term memory, wide-based ataxic gait, left abducens palsy	1 day	Overall survival
9	Vilibic-Cavlek <i>et al.</i> <sup>23</sup>	TBEV	Fever up to 39°C, headache, vomiting, pleocytosis	9 days	Overall survival
10	Colman <i>et al.</i> <sup>24</sup>	POWV	Mild headache, trouble dressing, acute confusion, new-onset blurred vision, decreased appetite, emesis, lethargy, persistent seizure activity, right-sided weakness	36 days	Overall survival
11	Dumic <i>et al.</i> <sup>25</sup>	POWV	Fever (38.8°C), Somnolence but arousable, meningeal signs, asterixis, encephalopathy with inattention, absence of spontaneous speech and inability to follow commands, negative motor signs, thrombocytopenia, hypokalaemia, elevated CSF protein, CSF lymphocytosis, negative head CT and brain MRI, respiratory failure	1 day	Overall survival
12	Kakoullis <i>et al.</i> <sup>26</sup>	POWV	Malaise, nausea, sore throat, high fever, headache, disorientation, cranial nerve palsies, convulsions, obtundation, tremors, twitching, nystagmus, hallucinations, hemiparesis, quadriplegia, respiratory failure, cognitive deficits, memory loss, hearing impairment, aphasia, muscle wasting, dysarthria, apnoea, psychosis, spastic hemiplegia	4 days	Death
13	Birge <i>et al.</i> <sup>27</sup>	POWV	Dizziness, fever (up to 103°F or 39.4°C), chills, malaise, nausea, occasional confusion with slurred speech, mild neck tenderness, alert, leukocytosis (neutrophil predominance), CSF abnormalities (leukocytosis, erythrocytes, elevated protein), laboured breathing, unresponsiveness, absent deep tendon reflexes, ocular deviation, positive Babinski response, bilateral flaccid paralysis of extremities	3 days	Death after 13 days

(Continued)

**Table 2.** (Continued)

S.No.	Author	Cause of disease	Symptoms	Time from onset of symptoms to diagnosis	Survival
14	Tavakoli <i>et al.</i> <sup>28</sup>	POWV	Fatigue, fever, bilateral maculopapular palmar rash, diplopia, dysarthria, weakness in the right arm and leg, leukocytosis, elevated protein in CSF, lymphocytic pleocytosis, reactive T-cell population in CSF, abnormal T2-weighted and FLAIR brain imaging, hyperintensities in the superior cerebellum, left pons, bilateral basal ganglia, restricted diffusion in the superior cerebellum suggesting ischaemic process, febrile (maximum temperature, 104.5°F or 40.3°C), obstructive hydrocephalus, external ventricular drain placement, worsening of signal abnormalities, markedly increased hydrocephalus, suboccipital craniotomy, severe meningoencephalitis, dense meningeal lymphoid infiltrate, lymphocytic venous invasion and destruction, loss of cerebellar Purkinje cells, microglial nodules, Bergmann gliosis, infiltration by activated microglia-macrophages	7 days	Death on day 17th
15	Henningsson <i>et al.</i> <sup>29</sup>	TBEV	Fever, neck pain, myalgia, difficulty walking, severe headache, pronounced fatigue, lumbar puncture revealing pleocytosis, difficulty walking, headache, high levels of serum TBEV IgM and IgG	8 days	Overall survival
16	Voulgari <i>et al.</i> <sup>30</sup>	TBEV	Occipital headaches, poor balance, tick bite history, Flu-like syndrome, negative serological testing for borreliosis and TBEV, febrile, neck stiffness, ataxia, unilateral visual loss in the right eye, non-granulomatous anterior uveitis, vitreous inflammation, retinal haemorrhages at the posterior pole	15 days	Overall survival
17	Yurchenko <i>et al.</i> <sup>31</sup>	TBEV	Occipital headaches, poor balance, tick bite history, Flu-like syndrome, negative serological testing for borreliosis and TBEV, febrile, neck stiffness, ataxia, unilateral visual loss in the right eye, non-granulomatous anterior uveitis, vitreous inflammation, retinal haemorrhages at the posterior pole, absence of macular oedema or papillitis	8 days	Overall survival
18	Divé <i>et al.</i> <sup>32</sup>	TBEV	Patient 1: Headache, fever, rapidly progressive tetraparesis, hypoesthesia below Th6 Patient 2: high fever, headache, back pain	N/A	Overall survival
19	Czarnowska <i>et al.</i> <sup>33</sup>	TBEV	Fever, dizziness, progressive left-sided hemiparesis, neck stiffness, lower motor neuron weakness in the upper limb, upper motor neuron weakness in the lower limb (more dominant on the left side), dysarthria, right sixth cranial nerve palsy, head droop due to weakness of the neck muscles, rapidly progressive deterioration of clinical condition, Increased weakness in limbs	3 days	Overall survival
20	Cavanaugh <i>et al.</i> <sup>34</sup>	POWV	Fever, altered mental status, hypotension, oliguria, tick bite ( <i>I. scapularis</i> ), prophylactic doxycycline (200 mg), embedded tick removal (left shoulder), myalgias, chills, erythema migrans rash (left scapula), visual hallucinations, confusion	14 days	Death
21	Allgaier <i>et al.</i> <sup>35</sup>	POWV	Nausea, vomiting, headache, acute onset of confusion, fever, haematologic abnormalities (elevated leukocytes, neutrophilia), metabolic abnormalities (elevated blood urea nitrogen, creatinine), supple neck, no rash, no focal neurologic deficits, short-term memory deficit, temporal lobe seizures	2 days	Overall survival

*(Continued)*

**Table 2.** (Continued)

S.No.	Author	Cause of disease	Symptoms	Time from onset of symptoms to diagnosis	Survival
22	Neill <i>et al.</i> <sup>36</sup>	TBEV	Fever, peripheral leukocytosis, elevated CRP, pleocytosis in CSF, breathlessness, drowsiness, dysarthria, interrupted saccades, difficulty with alternating lateral tongue movements, pout reflex, brisk jaw jerk, normal upper limb tone, reduced tone in lower limbs, bilateral proximal muscle weakness (hip and knee flexors), distal limb power less affected, areflexia, bilateral flexor plantars, dermatomal sensory loss (L2 to L5 on the left), respiratory muscle weakness, intubation, long-segment myelitis on brain and spinal cord MRI, preganglionic lesion indicated by neurophysiology tests, rhombencephalitis, myeloradiculitis, positive for TBEV RNA in serum and urine, positive for TBEV IgG in serum and CSF	10 days	Overall survival
23	Weinmayr <i>et al.</i> <sup>37</sup>	TBEV	Fever, headache, nausea, vomiting, fatigue, mild hypoesthesia on both sides of the forehead	N/A	Overall survival
24	Kristiansen <sup>38</sup>	TBEV	N/A	N/A	Overall survival
25	Boyer <i>et al.</i> <sup>39</sup>	TBEV	Asymptomatic during the second consultation, no neurological symptoms, resolution of the ulcerative lesion, no abnormalities in haemogram and liver function tests	24 days	Overall survival
26	Zachary <i>et al.</i> <sup>40</sup>	POWV	Fever, headache, progressive encephalopathy, chills, fatigue, weakness, nausea, intermittent episodes of vomiting, unsteady gait, decreased oral intake, increased frequency of urination, tremulousness of the arms and jaw, somnolence, nonverbal, unable to follow commands, brisk deep-tendon reflexes, nuchal rigidity, systolic ejection murmur (grade 2/6)	12 days	Overall survival
27	Velay <i>et al.</i> <sup>41</sup>	TBEV	Cerebral meningo-radicular encephalitis, evolving to deep cerebral nuclei and thalamic haemorrhagic transformation and cerebral atrophy	N/A	Overall survival
28	Lotrič-Furlan <i>et al.</i> <sup>42</sup>	TBEV	Fever, severe headache, nausea, dry cough, malaise, intense myalgia, arthralgia, headache	N/A	Overall survival
29	Pogorzelski <i>et al.</i> <sup>43</sup>	TBEV	Mild fever, general weakness, muscle pains, headache, neck pains, pulsating noise in the head, palatal myoclonus, rhinophonia, difficulty speaking, difficulty swallowing	N/A	Overall survival
30	Cimperman <i>et al.</i> <sup>44</sup>	TBEV	N/A	N/A	N/A
31	McNair and Brown <sup>45</sup>	TBEV	Headache, weakness in the right arm, photophobia, anorexia, numbness around the nose, flushed appearance, vomiting, numbness to light touch and pin-prick over the nose, right arm and shoulder, reduced power in all right arm movements, absent biceps and supinator reflexes on the right side, reduced triceps reflex, drowsiness, confusion, neck stiffness, loss of power in the right arm, bilateral facial and ocular palsies, increased CSF pressure, elevated white cell count in CSF (95% lymphocytes), elevated protein concentration in CSF, hearing loss in the right ear	25 days	Overall survival
32	Gils <i>et al.</i> <sup>46</sup>	TBEV	Flu-like syndrome, nausea, vomiting, rigidity of neck and shoulders, mild meningeal irritation, confusion, encephalopathy, dyskinesia of the limbs (tremor), tongue tremor, hyperexcitability symptoms, residual symptoms of hyperexcitability	N/A	Overall survival

(Continued)

**Table 2.** (Continued)

S.No.	Author	Cause of disease	Symptoms	Time from onset of symptoms to diagnosis	Survival
33	Agergaard <i>et al.</i> <sup>47</sup>	TBEV	Case 1: Meningoencephalitis Case 2: Fever, fatigue, influenza like symptoms Case 3: Headache, nausea, fatigue, photophobia, fever, dehydration, poor general condition	N/A	Overall survival
34	Weststrate <i>et al.</i> <sup>48</sup>	TBEV	Tinnitus, malaise, vomiting, muscle aches, headache, fever, erythema migrans (absent in this case), signs of inflammation, CRP elevation, leukocytosis, mononuclear cells in CSF, polynuclear cells in CSF, elevated glucose in CSF, elevated protein in CSF	N/A	Overall survival
35	Iff <i>et al.</i> <sup>49</sup>	TBEV	Headache, nausea, fever, tick bite, myalgia, refusal to walk, tender muscles on palpation, fever (39°C), leukopenia, increased concentrations of alanine aminotransferase	5 days	Overall survival
36	Zajkowska <i>et al.</i> <sup>50</sup>	TBEV	Fever, vomiting, irritability, bulging fontanelle, pleocytosis, elevated serum CRP concentration (46 mg/l), partial secondary generalized seizure, intermittent slowing in the right parieto-temporal region in EEG, T2-weighted cortico-subcortical hyperintensity in MRI, contrast enhancement in both frontal lobes in MRI, leptomeningeal enhancement in MRI, repetitive seizures, interictal series of sharp waves in the right parieto-temporal region in EEG	2 days	Overall survival
37	Arnež <i>et al.</i> <sup>51</sup>	TBEV	N/A	N/A	N/A
38	Ananthan <i>et al.</i> <sup>52</sup>	POWV	Severe occipital headaches, nausea, vomiting, afebrile, high sensitive CRP within normal range (2.2 mg/l), slightly elevated estimated sedimentation rate (24 mm/h)	4 days	Overall survival
39	Choi <i>et al.</i> <sup>53</sup>	POWV	Fever, chill, arthralgia, myalgia, rash, diarrhoea, sudden-onset left-sided weakness, declining level of consciousness, intubation, transfer to a tertiary medical centre, right thalamic lesion on initial MRI, restricted diffusion on ADC map, bilateral thalamic lesions on second MRI	2 days	Overall survival
40	Zajkowska <i>et al.</i> <sup>54</sup>	TBEV	Fever (40°C), headache, vomiting, drowsiness, frequent tick bites, facial nerve palsy (seventh nerve), tremor in facial muscles (left side), muscle weakness in left upper and lower limbs, positive meningeal signs, testing of CSF revealing inflammatory features	1 week	Overall survival
41	Herpe <i>et al.</i> <sup>55</sup>	TBEV	N/A	N/A	
42	Bologheanu <i>et al.</i> <sup>56</sup>	TBEV	Fever, headache, vomiting, drowsiness, tick bite history 2–3 weeks prior to symptom onset, history of TBE vaccination	7 days	Overall survival
43	Pessa <i>et al.</i> <sup>57</sup>	TBEV	N/A	N/A	Overall survival
44	de Graaf <i>et al.</i> <sup>58</sup>	TBEV	Malaise and fatigue tremors, slow speech, weakness and fatigue and fever nausea and vomiting	24 days	Overall survival
45	Lessell and Collins <sup>59</sup>	POWV	Nausea, vomiting, diarrhoea, dizziness, diplopia, and incoordination followed within days by arm weakness, urinary retention, fever, delirium, and almost total ophthalmoplegia, anxiety, depression, impairment of recent memory, difficulty maintaining attention, bifacial weakness, ophthalmoplegia, dysarthria, and bilateral arm and neck weakness	19 days	Overall survival
46	Takashima <sup>60</sup>	TBEV	Double vision, convulsions, motor paralysis of the arms and neck	3 years	Overall survival
47	Waldvogel <i>et al.</i> <sup>61</sup>	TBEV	Low-grade fever, nausea, vomiting and mild headache, lethargic and disoriented, marked nuchal rigidity- and decreased peripheral left-sided reflexes	N/A	Overall survival

*(Continued)*

**Table 2.** (Continued)

S.No.	Author	Cause of disease	Symptoms	Time from onset of symptoms to diagnosis	Survival
48	Fomsgaard <i>et al.</i> <sup>62</sup>	TBEV	Fever and other influenza-like symptoms as well as arthritis	2 weeks	Overall survival
49	Tajima <i>et al.</i> <sup>63</sup>	TBEV	N/A	N/A	N/A
50	Rácz <i>et al.</i> <sup>64</sup>	TBEV	N/A	N/A	N/A
51	Cruciatti <i>et al.</i> <sup>65</sup>	TBEV	Case 1: Ever, headache, vomiting, pain in the shoulders and neck stiffness, fever (37.5°C), flu-like symptoms and back pain of 3 days duration, neck stiffness and paralysis of upper limbs. Case 2: Fever, headache, nausea, asthenia, pain in the neck, diffuse myalgia and weakness of the left side limbs. Case 3: Headache and vomiting, behavioural symptoms, like confusion and irritability	14–35 days	Overall survival
52	Enzinger <i>et al.</i> <sup>66</sup>	TBEV	Rapidly progressive and painful paresis of the left leg, pronounced diffuse paresis, hypoesthesia, and diminished tendon reflexes of the left lower extremity	N/A	Overall survival
53	Bender <sup>67</sup>	TBEV	Acute headache, nausea, and vomiting, he began to have dysarthria, diplopia, gait ataxia, and clumsiness in both hands	24 days	Overall survival
54	Hemmer <i>et al.</i> <sup>68</sup>	TBEV	Transient fever and headache difficulty in concentrating, apathy, and a strong urge to sleep, fever (temperature 39.2°C) and mental confusion. Somnolence, slurred speech, amnesic dysphasia, and impaired fine motor control, but no meningism, focal signs, pyramidal tract or sensation impairment	14 days	Overall survival
55	Mázló and Szántó <sup>69</sup>	TBEV	Fever, headache, nausea, speech and vision disturbances, and weakness in the left extremity	20 days	Overall survival
56	Raval <i>et al.</i> <sup>70</sup>	POWV	Case 1: Significant headache for 2 days and one episode of seizure. Case 2: Fevers, headaches and dizziness Case 3: Progressive headaches, body aches, high-grade fever, and altered mental status. Case 4: Progressive weak-ness, headaches and fevers	N/A	Overall survival
57	Piantadosi <i>et al.</i> <sup>71</sup>	POWV	Case 1: Sudden onset of dizziness followed by nausea and vomiting Case 2: Right eye pain and visual blurring Case 3: Vomiting, confusion, and fever Case 4: Confusion, vomiting, diarrhoea, and fever Case 5: Fever, confusion, headache, and vomiting Case 6: Fever and myalgias Case 7: Fever and headache Case 8: Headache, fatigue, diplopia, and a diffuse rash over his trunk and extremities	N/A	Overall survival
58	CDC <sup>72</sup>	POWV	N/A	N/A	Overall survival
59	Botelho-Nevers <i>et al.</i> <sup>73</sup>	TBEV	Headache, cervicobrachial neuralgia, and meningoencephalitis	N/A	
60	Ponfick <i>et al.</i> <sup>74</sup>	TBEV	1. Fever, a left-sided hemiparesis developed, followed by tetraplegia (MRC 1/5) with vanished deep tendon reflexes, and rapid respiratory failure	N/A	Overall survival
61	Kuivanen <i>et al.</i> <sup>75</sup>	TBEV	Case 1: Ever onset. Sudden-onset headache, left arm numbness, and impaired vision. Case 2: Persistent fever, tetraparesis urinary retention	N/A	Overall survival

(Continued)

**Table 2.** (Continued)

S.No.	Author	Cause of disease	Symptoms	Time from onset of symptoms to diagnosis	Survival
62	Sung <i>et al.</i> <sup>76</sup>	POWV	Case 1: Sore throat and influenza-like symptoms: fever, eye pain, lateral gaze palsy, ataxia, dysarthria, stomach pain, and neck stiffness. Case 2: Lower extremity weakness and altered mental status, headache, fever, chills, and bilateral ankle pain had developed; headache, fever, chills, and bilateral ankle pain had developed; bilateral leg weakness, confusion, and diplopia	N/A	Overall survival
63	Zaki <sup>77</sup>	TBEV	Fever, headache, generalized, arthralgia, anorexia, vomiting	N/A	Overall survival
64	Skarpaas <i>et al.</i> <sup>78</sup>	TBEV	Case 1: Dizzy and weak, had a headache, chills, and fever Case 2: Fever, increasing headache, nausea, and vomiting. Case 3: Headache was intense and accompanied by nausea and vomiting	6 days–5 weeks	
65	Mease <sup>79</sup>	TBEV	Case 1: Left-sided hemiparesis, which appeared on the day of presentation. This is consistent with the published literature, with focal, unilateral, and upper body areas being the most commonly affected by neurological abnormalities, Case 2: Right-sided frontal headache	1 week 6 day	Overall survival
66	Schultze <i>et al.</i> <sup>80</sup>	TBEV	Leucocytopenia and thrombocytopenia, intermittent fever, headache, loss of appetite, malaise, photophobia, vertigo upon rising, and unstable gait		
67	Voshii <i>et al.</i> <sup>81</sup>	TBEV	N/A	N/A	N/A
68	Mohareb <i>et al.</i> <sup>82</sup>	TBEV	Case 1: High fever (40°C) and malaise. The patient's temperature returned to normal (4 days after admission) and then about a week later, the patient's condition again deteriorated, with fever, headache, stiff neck, sore throat, nausea, vomiting and a depressed mood. Case 2: Headache, fatigue, nausea and vomiting. Physical examination revealed stiff neck, muscle soreness, conjunctivitis, stupor and abnormal reflexes with pain in joints Case 3: Ever (37.5–38°C), considerable numbness in the muscles and weakness. Physical examination revealed mild neck stiffness, mild left hemiplegia and hypaesthesia of the limbs	4 days after admission	Overall survival
69	Reuksen <i>et al.</i> <sup>83</sup>	TBEV	Case 1: Dizziness, non-productive cough and fear of noise, she had, on the day of admission, an acute fever (39°C) accompanied with severe headache and muscle pain. Muscle weakness, nausea and vertigo were also present Case 2: Severe headache, fever and fatigue. He also complained about impaired hearing and blurred vision	N/A	Overall survival
70	Ergunay <i>et al.</i> <sup>84</sup>	TBEV	Overall symptoms of meningitis, encephalitis and gastrointestinal	N/A	Overall survival
71	Kleiter <i>et al.</i> <sup>85</sup>	TBEV	N/A	N/A	Overall survival
72	Chaudhuri and Růžek <sup>86</sup>	TBEV	Severe fatigue and lower limb myalgia	N/A	Overall survival
73	Doyle <i>et al.</i> <sup>87</sup>	TBEV	N/A	N/A	N/A
74	Nord and Goldberg <sup>88</sup>	POWV	Altered mental status, fever (104°F), new chorioretinal lesions in a linear streak-like distribution, increased anterior chamber and vitreous cells, hypo-autofluorescent streaks in fundus autofluorescence, multifocal choroidal inflammation in fluorescein angiography	N/A	Overall survival
75	Four <i>et al.</i> <sup>89</sup>	TBEV	Low grade fever, general discomfort, holointracranial headache, nauseated photophobia	N/A	Overall survival

(Continued)

**Table 2.** (Continued)

S.No.	Author	Cause of disease	Symptoms	Time from onset of symptoms to diagnosis	Survival
76	Tanaka <i>et al.</i> <sup>90</sup>	TBEV	Fever (39°C), headache, nausea, meningitis, restlessness, disturbance of consciousness, ataxic breathing, improvement with steroid pulse therapy, tracheal intubation, respirator use, gradual improvement, discharged on day 24 without sequelae	3 days	Overall survival
77	Montvydaite <i>et al.</i> <sup>91</sup>	TBEV	Fever followed by proximal muscle pain and weakness	N/A	
78	Hockicková <i>et al.</i> <sup>92</sup>	TBEV	N/A	N/A	N/A
79	de Bruijn <i>et al.</i> <sup>93</sup>	TBEV	Cough, headache, malaise, polyarthritis, rash, and glomerulonephritis, subsequent development of balance problems, fever, progressive headache, alert on neurological examination, no neurological deficits observed, reported neck pain radiating to the left arm, unsteady on feet	1 day	Overall survival
80	Walder <i>et al.</i> <sup>94</sup>	TBEV	N/A	N/A	N/A
81	McLean and Donohue <sup>95</sup>	POWV	Right-sided headache, drowsiness, fever, twitching, tremors, nystagmus, followed by worsening mentation, neck stiffness, left-sided hemiplegia, ataxia	N/A	Death on day 4
82	Goldfield <i>et al.</i> <sup>96</sup>	POWV	Severe retro-orbital headache, hearing loss, dizziness, lethargy, delirium	N/A	Overall survival
83	Smith <i>et al.</i> <sup>97</sup>	POWV	Case 1: Sudden-onset fever 39–40°C, headache, three generalized tonic-clonic seizures lasting 5 min each Case 2: Sudden onset of URI, sore throat, fever 39°C, a single convulsion followed by status epilepticus Case 3: Fever, convulsions, somnolence, disorientation, severe headache	8 days 12 days 12 h	Overall survival
84	Rossier <i>et al.</i> <sup>98</sup>	POWV	Headache, malaise, anorexia, vomiting, fever, somnolence, neck stiffness, followed by stupor, seizures. Progressed to coma, right gaze deviation, left facial palsy, and bilateral pyramidal tract signs	4 days	Overall survival
85	Wilson <i>et al.</i> <sup>99</sup>	POWV	4-Day history of anorexia, lethargy, fever 38–39°C, rash	1 month	Overall survival
86	Parington <i>et al.</i> <sup>100</sup>	POWV	3-Day history of fever, vomiting, increasing lethargy, headache	2 month	Overall survival
87	Embil <i>et al.</i> <sup>101</sup>	POWV	Malaise, olfactory hallucination, reduced appetite, seizures, fever	12 h	Overall survival
88	Fitch and Artsob <sup>102</sup>	POWV	4-Day history of malaise, fever, intermittent headache, vomiting	N/A	Overall survival
89	Gholam <i>et al.</i> <sup>103</sup>	POWV	Headache, fever, expressive and nominal dysphasia, mild right facial weakness	11 days	Death
90	Courtney <i>et al.</i> <sup>104</sup>	POWV	Case 1: Fever, generalized muscle weakness, somnolence, diarrhoea, anorexia Case 2: Agitation, ataxia, bilateral lateral gaze palsy, dysarthria, loss of balance, visual disturbance, fever Case 3: Fever, headache, vomiting, somnolence, confusion, bilateral hand twitching, muscle weakness, pronounced lip smacking. Case 4: Somnolence, severe headache, increasing confusion, progressive bilateral leg weakness, slow speech, memory loss, wide-based gait	3 month 19 days 3 days 19 days	Overall survival

(Continued)



**Table 2.** (Continued)

S.No.	Author	Cause of disease	Symptoms	Time from onset of symptoms to diagnosis	Survival
91	Hinten <i>et al.</i> <sup>105</sup>	POWV	Case 1: Somnolence, AMS, generalized muscle weakness progressing to left-sided hemiplegia, encephalopathy, renal insufficiency, anaemia. Case 2: Ataxia, bilateral lateral gaze palsy, dysarthria, AMS, generalized muscle weakness, complete ophthalmoplegia Case 3: Fever 38.5°C, headache, vomiting, somnolence, confusion, inability to walk, bilateral hand twitching, bilateral upper extremity weakness, pronounced lip-smacking Case 4: Headache, fever 40.5°C, myalgias, confusion, progressive weakness with inability to speak or walk, combative, tremors Case 5: Somnolence, severe headache, increasing confusion, slow speech, short-term memory loss Case 6: Abdominal pain, vomiting, fever 38.7°C, chills, lethargy Case 7: Fever 39.2°C, diplopia, acute onset of proximal muscle weakness in all extremities (upper > lower), paralysis, respiratory failure requiring mechanical ventilation Case 8: Fever, headache, AMS, stiff neck, generalized muscle weakness Case 9: Fever, headache, AMS, stiff neck, muscle pain, generalized muscle weakness	3 days 19 days 3 days 5 days 19 days 12 days 10 days 2 days N/A	Overall survival
92	Trépanier <i>et al.</i> <sup>106</sup>	POWV	Fever, AMS, disorientated with incoherent speech, dizziness, headache	N/A	Overall survival
93	Hicar <i>et al.</i> <sup>107</sup>	POWV	Headache, abdominal pain, emesis, fever to 39.4°C, nuchal rigidity	N/A	Overall survival
94	Tutolo <i>et al.</i> <sup>108</sup>	POWV	Fever, vomiting, right-sided facial twitching that progressed to seizures	4 days	Overall survival
95	Sanderson <i>et al.</i> <sup>109</sup>	POWV	Right abducens nerve palsy, mild left-sided pyramidal weakness, erythematous mark on right shoulder	8 days	Overall survival
96	Patel <i>et al.</i> <sup>110</sup>	POWV	Fever 41.1°C, somnolence, neck stiffness, diffuse motor weakness, increased tone and cogwheel rigidity, nonconvulsive status epilepticus	11 days	Overall survival
97	Picheca <i>et al.</i> <sup>111</sup>	POWV	Nausea, vomiting, abdominal pain, diplopia, ataxia, dysarthria, respiratory distress, weakness progressing to flaccid paralysis (upper > lower) with preserved sensation	1 month	N/A
98	Koester <i>et al.</i> <sup>112</sup>	POWV	History of headache, photophobia, fever to 38.3°C, lethargy, poor oral intake, diffuse abdominal pain, vomiting	4 days	Overall survival
99	Taylor <i>et al.</i> <sup>113</sup>	POWV	Severe headache, fever, weakness, myalgias, chills, confusion, photophobia, nausea, diarrhoea	13 days	Overall survival
100	Kroopnick <i>et al.</i> <sup>114</sup>	POWV	Back pain, headache, vomiting, followed by acute agitation and confusion. Co-infected with anaplasma phagocytophilum	11 days	Death
101	Johnson <i>et al.</i> <sup>115</sup>	POWV	Case 1: Headache, recurrent fever, rapidly progressive weakness Case 2: Headache, encephalopathy, inability to follow commands, rigidity with saccades, vertical upgaze restriction	N/A N/A	Overall survival

ADC, Antibody–drug conjugates; AMS, Altered mental status; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, Computed tomography; EEG, Electroencephalogram; FLAIR, fluid-attenuated inversion recovery; MRC, Medical research council; MRI, Magnetic Resonance Imaging; N/A, not available; POWV, Powassan virus; TBE, tick-borne encephalitis; TBEV, tick-borne encephalitis virus; URI, Upper respiratory infection; WBC, white blood cells.

Japan, among others. This extensive geographical representation greatly enriches our potential for developing a thorough comprehension of how the infectious agent impacts distinct populations. The gender distribution observed across studies,

wherein some investigations specifically focus on males, females, or both genders, adds a layer of complexity to our understanding. The age spectrum underscores the broad demographic diversity encapsulated in the data. Notably, specific

**Table 3.** Prevalence of patients' neurological complications.

Neurological manifestation	N (%)
Mental status deterioration	3 (2.06)
Slurred speech	5 (3.44)
Meningoencephalitis	15 (10.34)
Aphasia	1 (0.68)
Dementia	3 (2.06)
Dysarthria	6 (4.13)
Severe occipital headache	33 (22.75)
Poor balance	9 (6.20)
Tetraparesis	8 (5.517)
Visual hallucinations	7 (4.8)
Meningismus associated with nystagmus	3 (2.06)
Monoplegia	1 (0.689)
Bulging fontanelle	2 (1.37)
Facial nerve palsy	6 (4.13)
Peripheral polyneuropathy	1 (0.689)
Neuralgic amyotrophy	1 (0.689)
Diplopia	1 (0.689)
Ophthalmoplegia	2 (1.37)
Flaccid paresis	10 (6.8)
Seizure	12 (8.27)
Haemorrhage with subdural haematoma	2 (1.37)
Absent deep tendon reflexes	6 (4.13)
Proximal flaccid tetraplegia	6 (4.13)
Wide gait	3 (2.06)
Cervicobrachial neuralgia	1 (0.689)
Leptomeningeal	2 (1.37)
Cranial nerve palsy	2 (1.37)

cases within the studied populations provide in-depth age-related information.

It is imperative to acknowledge the variability in symptom reporting across studies, resulting in disparate patient counts for each symptom.

Collectively, the data from these studies encompass 135 patients exhibiting neurological symptoms associated with either the Powassan or TBEV infection, as outlined in Table 3. The possible window for contracting the POWV spans from as soon as 1 week to as long as 1 month after exposure. Following infection, there is an incubation period lasting 2–4 weeks before observable symptoms manifest. In contrast, for TBEV, the incubation period ranges from 1 week to 3 weeks. However, the duration between the onset of these symptoms and the formal diagnosis exhibits variability, contingent upon factors such as diagnostic test availability, the strength of healthcare infrastructure, and the level of awareness among healthcare providers. Consequently, the time required to confirm a POWV infection may vary across diverse geographical locations and healthcare settings.

Among the various symptoms observed, a severe occipital headache emerged as the most prevalent, affecting approximately 33(22.75%) (Table 3) of the patients. This particular finding holds critical importance as these intense headaches can substantially diminish patients' quality of life and necessitate prompt medical intervention. Following closely, meningoencephalitis was identified in approximately 15(10.34%) of the patients. Meningoencephalitis characterized by inflammation of the brain and meninges was diagnosed. Meningoencephalitis is a severe condition that demands urgent medical treatment to prevent potential complications and mitigate the risk of long-term neurological deficits. Seizure was observed in 12(8.27%). Flaccid paresis refers to the weakening or loss of muscle tone, a condition that can lead to varying degrees of paralysis was observed in 10(6.8%) The implications of flaccid paresis can be particularly debilitating for patients, as it can severely hamper their ability to perform daily tasks and maintain their independence (Table 3).

Additionally, poor balance was reported in approximately 9(6.20%) of patients, potentially indicating impairment within the cerebellar or vestibular systems. These symptoms underscore the complexity of neurological involvement in the infection and highlight the need for multidisciplinary approaches to assessment and management. Wide gait was observed in approximately 3(2.06%) (Table 3) of the patients, suggesting difficulties in walking. Accurate diagnosis and

targeted interventions are essential to address the underlying causes of these walking difficulties and to improve the patient's overall mobility and functional independence.

Several other notable neurological symptoms were observed among the patients. Facial nerve palsy and absent deep tendon reflexes each was reported in 6(4.13%) of the cases. Facial nerve palsy signifies disruptions in normal neurological functioning and can range from mild to severe manifestations. The absence of deep tendon reflexes also raises concerns about potential nerve or muscle involvement and requires thorough evaluation.

Dysarthria, characterized by difficulty in articulating speech was observed in 6(4.13%) of the cases. Similarly, slurred speech affected around 5 (3.44%) (Table 3) of the cases, providing further insight into the infection's impact on regions associated with speech production and motor control.

### Overall survival

Among 135 patients, 9 cases (6.66%) resulted in fatal outcomes attributed to POWV infection, as outlined in Table 2. Specifically, a 63-year-old immunocompromised male with follicular lymphoma undergoing maintenance rituximab therapy passed away on the 14th day, according to Solomon *et al.* Additionally, Birge *et al.* reported the death of a 67-year-old woman, who had a medical history notable for colon cancer, on the 13th day. Tavakoli *et al.* documented the demise of a 62-year-old man with a 4-year history of chronic lymphocytic leukaemia–small lymphocytic lymphoma (CLL–SLL) on the 17th day. McLean *et al.* recorded the tragic passing of a 5-year-old boy on the fourth day of hospitalization. Gholam *et al.* documented the demise of a previously healthy 64-year-old man who had reported a headache persisting for the last 3 days, accompanied by a fever (38.9°C). Additionally, he had been experiencing drowsiness and slurred speech in the preceding day. The cause of death, as established through autopsy, was identified as a substantial pulmonary embolism. Kroopnick *et al.*, Yu *et al.*, Kakoullis *et al.* and Cavanaugh *et al.* have independently documented cases resulting in mortality attributed to POWV. The overall survival rate remains at 94.81%. Nevertheless, several patients encountered complications, including paralysis, tremors, cognitive defects and other issues, detailed in Table 3.

### Discussion

The POWV, a tick-borne flavivirus, is a significant public health concern due to its potential to cause severe neuroinvasive disease in humans. In our comprehensive review of 101 studies discussing symptoms or diseases similar to those associated with either POWV or TBEV with concurrent neurological manifestations, our findings indicate that individuals of any age group can acquire POWV infection, but elderly individuals exhibit a higher susceptibility to neuroinvasive illness, with a slight male predominance. Those showing symptoms undergo an incubation phase lasting 2–4 weeks, followed by a febrile prodrome characterized by manifestations such as sore throat, sleepiness, headaches, and confusion. Timely diagnosis and intervention are imperative to mitigate complications and avert long-term neurological deficits. The presence of various other neurological symptoms, such as dysarthria, facial nerve palsy, seizure, and absent deep tendon reflexes, further emphasizes the complexity of POWV infection and its diverse effects on the CNS. These symptoms can lead to significant disability and require comprehensive management by healthcare professionals. In serious cases, side effects of ataxia, quake, muscle shortcoming, oculomotor and pseudobulbar paralysis have been depicted.<sup>15</sup> In addition to neurological complications, eye involvement, though rare, can present with symptoms such as non-granulomatous anterior uveitis, vitreous inflammation, and retinal haemorrhages, along with bilateral multifocal chorioretinitis.<sup>30,88</sup>

According to a case report, a 58-year-old man visited the emergency department due to occipital headaches and balance problems, followed by vision loss in his right eye 6 weeks after reporting a tick bite.<sup>30</sup> His eye examination showed non-granulomatous anterior uveitis, vitreous inflammation and retinal haemorrhages without macular swelling or papillitis.<sup>30</sup> Another case, involved a 51-year-old man who had a history of chronic bilateral noninfectious anterior and sporadic uveitis.<sup>88</sup> He was receiving treatment involving mycophenolate mofetil and adalimumab. In May 2017, he underwent a sudden alteration in his mental state accompanied by a high fever of 104°. Subsequent lumbar puncture confirmed the presence of distinct antibodies (IgM and neutralizing IgG) specific to the POWV.<sup>88</sup> This finding indicated that the virus was responsible for inducing bilateral multifocal chorioretinitis characterized

by linear clustering within his eyes, resembling the pattern observed in eyes affected by the West Nile Virus.

Mendoza *et al.* conducted a retrospective study at Mayo Clinic, encompassing 16 cases of neuroinvasive POWV. The study revealed a slight predilection for older and male patients. The diverse clinical presentations included rhombencephalitis (6), isolated meningitis (4), meningoencephalitis (3), meningoencephalomyelitis (2), and opsoclonus myoclonus syndrome (1). The diagnosis was typically established around a median of 18 days after the onset of symptoms. The observed mortality rate was 18.8%, and a substantial 72.7% of survivors exhibited enduring neurologic deficits.<sup>116</sup> This study stands as a comprehensive exploration of neuroinvasive POWV cases, emphasizing the importance of recognizing varied presentations and potential long-term consequences.

Despite the increasing number of cases and the severity of neurological effects related to Powassan infection, substantial obstacles persist in both diagnosing and managing this virus. One key hurdle is the varied clinical presentation, which can imitate other neurological disorders or arboviral infections. Furthermore, currently available diagnostic techniques for POWV lack specificity that matches the intricacy and gravity of the disease. As a general principle, there are no distinctive clinical indicators to differentiate POWV disease from other arboviruses.<sup>3</sup> Notably, the brainstem, spinal cord, cerebellum, cerebral cortex and basal ganglia have all been noted as areas of specific damage, although previous reports did not incorporate a semi-quantitative evaluation of inflammation. Less commonly, instances of inflammation in the thalamus, hippocampus and white matter have been documented.<sup>15</sup> Interestingly, only one case reported an adverse outcome, tragically resulting in fatality. Our observations indicate that these symptoms often follow a self-limiting trajectory, which corresponds with existing research emphasizing the impact of factors such as the patient's age, occupation, epidemiological context, and underlying health conditions on the outcome.

Medical professionals in areas where POWV is prevalent should possess knowledge about the virus and consider conducting serologic tests on blood or cerebrospinal fluid (CSF) specimens at state or other laboratories equipped to handle

POWV testing. When POWV RNA is detected, the pathological and molecular findings imply a combination of direct viral-induced CNS neuronal damage along with broad-ranging lymphocytic inflammation and microgliosis involving the leptomeninges and brain tissue.<sup>20</sup> It is essential for medical practitioners to remain attentive in identifying these signs, particularly in regions like the USA with documented POWV prevalence. Recognizing exposure to ticks is pivotal in facilitating the diagnosis. Additionally, there is an apparent expansion in the geographic distribution of POWV infections. Timely identification and suitable treatment have the potential to notably enhance patient outcomes. By recognizing the pivotal elements that contribute to the diversity in symptoms, healthcare providers can customize their strategies to offer more individualized and efficient care for those affected.

This study has certain limitations that warrant acknowledgment. Firstly, the information included in each case relies on the reporting from individual studies, and in several instances, the data were incomplete. The literature search strategy was crafted to comprehensively address neurological manifestations, not strictly tied to the POWV. It's important to note that the term 'tick-borne flaviviruses' is occasionally used as an umbrella term, encompassing both the POWV and those linked to TBEV. Moreover, despite the absence of reported POWV cases in the EU, European countries were included based on studies examining symptoms or diseases similar to those associated with TBEV.

### Conclusion

In conclusion, POWV is an emerging tick-borne flavivirus that can cause severe neuroinvasive disease in humans. The neurological presentations associated with Powassan infection are diverse and can have debilitating effects on patients. Early recognition of symptoms, especially severe occipital headaches and flaccid paresis, is critical to prompt appropriate diagnostic testing and intervention. Therefore, further research is imperative to develop more accurate diagnostic tools, effective treatments and potentially a vaccine. Public health efforts to control tick populations and educate the public about the risks of POWV are essential to reduce the incidence of infection. Further, subsequent research endeavours could

involve conducting more focused studies in European regions aimed at discerning the prevalence or absence of the POWV. By fostering collaboration among researchers, healthcare professionals, and public health authorities, we can advance our understanding of POWV and develop strategies to mitigate its impact on affected communities.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Areeba Fareed:** Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing.

**Samia Rohail:** Conceptualization; Methodology; Writing – original draft.

**Ushna Zameer:** Data curation; Writing – original draft.

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**Syed Muhammad Muneeb Akhtar:** Data curation; Software; Writing – review & editing.

**Waniyah Masood:** Investigation; Writing – review & editing.

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## Supplemental material

Supplemental material for this article is available online.

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