



ORIGINAL ARTICLE

The spectrum of central nervous system involvement in Whipple's disease

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Abstract

Background and purpose: To assess the clinical spectrum of central nervous system (CNS) involvement as well as cerebrospinal fluid (CSF) and neuroimaging findings in patients with Whipple's disease (WD) and to analyze the association of neurological symptoms with CSF and imaging findings.

Methods: Neurological involvement was retrospectively analyzed in a series of 36 patients diagnosed with WD at a single center between 1992 and 2019. Findings of 81 comprehensive CSF examinations from 36 patients, including polymerase chain reaction (PCR) tests for *Tropheryma whipplei* (TW) in CSF from 35 patients, were systematically evaluated. The prevalence of ischemic stroke in patients with WD was compared to a matched control cohort.

Results: Neurological symptoms occurred in 23 of 36 (63.9%) patients, with cognitive, motor, and oculomotor dysfunction being most frequent. TW was detected by PCR in CSF of 13 of 22 (59.1%) patients with and four of 13 (30.8%, $p = 0.0496$) patients without neurological symptoms. Total CSF protein ($p = 0.044$) and lactate ($p = 0.035$) were moderately elevated in WD with neurologic symptoms compared with WD without. No intrathecal immunoglobulin synthesis was observed. Three of 36 (8.3%) patients had hydrocephalus due to aqueductal stenosis. Patients with WD had an unexpectedly high prevalence of ischemic stroke (10/36, 27.7%) compared to matched controls (10/360, 3.2%).

Conclusions: Neurological involvement in patients with WD is common. Detection of TW DNA in CSF is only partly associated with neurological symptoms. Elevated CSF parameters suggest CNS parenchymal infection. Stroke is a hitherto underrecognized manifestation of WD. These findings suggest that mechanisms beyond CNS infection contribute to the spectrum of CNS involvement in WD.

KEYWORDS

bacterial infections, cerebrospinal fluid, embolic stroke, hydrocephalus, Whipple's disease

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INTRODUCTION

Whipple's disease (WD) is a rare (estimated prevalence 1–3 per 1 million) systemic infection caused by the actinobacterium *Tropheryma whipplei* (TW) [1–3]. Although WD is typically associated with gastrointestinal and arthritic symptoms, neurologic involvement has been reported in 22%–64% of patients [4–7] and confers an unfavorable prognosis [2, 8]. Susceptibility to systemic WD may be partly dependent on host factors [9–12]. The subsequent pathogenesis of neurological involvement in WD is not well understood. The present study investigated the associated neurological manifestations in patients suffering from any chronic infection with TW, comprising classical WD and other chronic localized infections.

Clinically, some patients with central nervous system (CNS) involvement of WD present with the highly WD-specific phenomenon of oculomasticatory myorhythmia (OMM), consisting of a ~1–2 Hz rhythmic unilateral masseter contraction combined with vertical converging nystagmus, which is frequently accompanied by supranuclear vertical gaze palsy (SVGP) [13–18]. The majority of patients, however, have been reported to have less specific and poorly defined symptoms, most frequently cognitive changes, movement disorders, eye movement disorders, and myoclonus, as well as signs of hypothalamic involvement, such as sleep pattern disturbance [2]. Although some patients with WD may show no signs of CNS infection despite positive polymerase chain reaction (PCR) testing in cerebrospinal fluid (CSF), others may develop an isolated CNS infection without systemic involvement [2]. To date, an explanation for this phenotypic variability is lacking [8, 19, 20]. Because the infecting TW strain does not seem to influence the course of the disease [21], distinct pathomechanisms could account for this heterogeneity, but have not been investigated comprehensively.

Infectious diseases of the CNS are typically associated with inflammatory changes in the CSF, such as an elevated cell count, blood–CSF barrier dysfunction, or an intrathecal immunoglobulin (Ig) synthesis. Nevertheless, systematic data on comprehensive CSF examinations, together with PCR results in patients with WD, are scarce. In addition, immune reconstitution inflammatory syndrome (IRIS) upon immunosuppressive treatment is another known source of WD symptoms but has not been well studied from a neurological perspective [22].

Here, we comprehensively investigated clinical, CSF, and imaging findings in a large monocentric cohort of 36 patients to characterize the spectrum and possible disease mechanisms of neurological involvement in WD.

PATIENTS AND METHODS

Patients

We retrospectively analyzed patients with WD diagnosed or treated at Charité–Universitätsmedizin Berlin between January 1992 and June 2019.

Inclusion criteria were age ≥ 18 years and a diagnosis of WD as defined by:

- Two of the following tests (PCR, immunohistochemical testing for TW, or periodic acid-Schiff (PAS) staining) from the same specimen were positive or
- Two of the following tests (PCR from sterile tissues and/or fluids, immunohistochemical testing for TW, or PAS staining) from different specimens were positive.

These inclusion criteria were adapted according to the definition of Günther et al. [23].

The diagnostic algorithm used for diagnosis is attached as a supplementary figure (Figure S1). Patients with only one positive test (e.g., PAS staining in duodenal biopsies) or asymptomatic carriers were excluded.

Patients with a diagnosis of other coexisting infectious diseases with potential CNS involvement were excluded. Furthermore, if available data were insufficient for retrospectively confirming a diagnosis of WD according to the above criteria, patients were excluded from the study. One patient had a positive TW PCR in blood and stool samples, which is currently not considered sufficient for diagnosis [23]. However, as transesophageal echocardiography showed clear signs of endocarditis, responding to antibiotics and no concurrent pathogens were detected, the diagnosis of TW endocarditis was apparent, and the patient was included in the study [9].

IRIS was defined as secondary clinical deterioration due to systemic or local inflammation while on effective antimicrobial treatment [24].

All digital and paper-based patient records available were screened, and information was collected and managed using REDCap electronic data capture tools [25]. Data collected included demographic characteristics, laboratory findings, clinical presentation, clinical course, microbiological results, PCR findings, and imaging data.

All described symptoms from patient histories and clinical examinations were recorded by annotating findings through the ontology-based terminology SnomedCT [26]. Neurological symptoms were grouped into dysfunctions of pyramidal motoric system, speech, oculomotoric movement, psychiatric, cognition and mnestic function, visual system, sleeping behavior, gait, reproductive function, sensory system, and occurrence of seizures, peripheral nerve affection, and other than above-described movement disorders.

Results of comprehensive CSF examinations, including CSF cell count, protein, lactate, glucose, presence of CSF-specific oligoclonal bands, and of a quantitative intrathecal IgG, IgM, or IgA synthesis were collected as were the results of TW PCR.

Detection of TW DNA was performed by TW-specific real-time PCR of the 16S rRNA gene of TW before 2003, between 2003 and 2011 by PCR of 16S rRNA and rpoB, and from 2012 only by rpoB gene PCR as described before [27]. All positive cases were confirmed by 16S rRNA-gene amplification and sequencing. PAS staining of biopsy specimens was performed by histological analysis. Specimens

included in the diagnostic process were duodenum, colon, antrum, skin, brain tissue, urine, blood, heart valve, lacrimal fluid, bone marrow, lymph node, CSF, or synovia.

All available brain magnetic resonance imaging (MRI) data were reviewed by an experienced neuroradiologist (E.S.).

In patients with a stroke, findings of neuroimaging, electrocardiograms, transthoracic and transesophageal echocardiography, duplex sonographies of the extra- and intracerebral arteries, and laboratory values were recorded, and the most likely etiology of the stroke classified according to the the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [28]. If the etiology could not be determined from available data, it was assigned as undetermined etiology.

For stroke prevalence, a comparison with an age- and sex-matched cohort was performed with data from 24,016 subjects of the GEDA 2014/2015-EHIS German health survey [29]. Nearest-neighbor matching with a 1:10 ratio was performed using the MatchIt package in R (R Foundation for Statistical Computing) [30].

Statistical analyses

Data were analyzed with the R language v3.6.3 (r-project.org/) using the Wilcoxon-Mann-Whitney test to compare medians between groups or Fisher exact test for proportions of a categorical outcome. Due to the exploratory nature of this study, no correction for multiple testing was performed. *p* values <0.05 were considered significant.

Ethics and regulations

This study was approved by the institutional review boards of Charité-Universitätsmedizin Berlin (EA4/153/20). All diagnostic procedures, including lumbar punctures, were performed as part of the routine diagnostic workup with the patients' written informed consent.

RESULTS

The spectrum of neurologic symptoms in WD

A total of 36 patients with a diagnosis of WD according to the study criteria were included in the analysis. Demographic characteristics and the frequency of clinical features of these 36 patients are shown in Table 1. In line with previous reports [4-7], median age at diagnosis was 55 years, and patients were predominantly male. Arthralgia was the most common clinical manifestation. Neurological signs and symptoms ranked before classical gastrointestinal manifestations such as weight loss or diarrhea. Immunosuppression prior to diagnosis was frequent (most frequent medications: steroids, azathioprine, and methotrexate), and six of the seven patients who developed an IRIS had previously received immunosuppression.

We first investigated the spectrum of reported neurologic signs and symptoms. A wide range of central and, less commonly, peripheral nervous system affections were observed. Cognitive impairment was most frequent and was characterized by mild to severe cognitive impairment, impaired short-term memory, temporal and spatial orientation disturbance, and attention and concentration deficits (Table 2). Pyramidal symptoms comprised monoparesis, hemiparesis

TABLE 1 Demographic and general clinical characteristics of patients with *Tropheryma whipplei* infection (*n* = 36)

Characteristic	Overall
Demographics	
Age at diagnosis, years, median [IQR]	55.50 [48.75–63.25]
Female:male (% male)	10:26 (72.2%)
Clinical features	
Arthralgia	32/36 (88.9%)
Any neurological symptoms	23/36 (63.9%)
Weight loss	22/36 (61.1%)
Diarrhea	20/36 (55.6%)
Lymphadenopathy	9/36 (25.0%)
Fever	7/36 (19.4%)
Immunosuppression prior to diagnosis	19/36 (52.8%)
Immune reconstitution inflammatory syndrome	7/36 (19.4%)

Note: Values are given as absolute numbers and percentages (in parentheses) unless otherwise indicated.

Abbreviation: IQR, interquartile range.

TABLE 2 Neurological symptoms in patients with *Tropheryma whipplei* infection (*n* = 23)

Symptom	Value, <i>n</i> (%)
Cognitive dysfunction	11 (47.8%)
Pyramidal motoric dysfunction	8 (34.8%)
Oculomotor dysfunction	7 (30.4%)
Other symptoms ^a	7 (30.4%)
Psychiatric symptoms	5 (21.7%)
Sleep disorder	5 (21.7%)
Seizures	5 (21.7%)
Abnormal gait	5 (21.7%)
Peripheral nerve affection	5 (21.7%)
Other movement disorders	4 (17.4%)
OMM and/or SVGP	4 (17.4%)
Speech disorder	3 (13.0%)
Visual system dysfunction	3 (13.0%)
Incontinence of urine or feces	3 (13.0%)
Sexual dysfunction	2 (8.7%)
Sensory symptoms	2 (8.7%)

Abbreviations: OMM, oculomasticatory myorhythmia; SVGP, supranuclear vertical gaze palsy.

^aOther symptoms include headache, hearing problem, tinnitus, nausea, vertigo, ptosis, dysphagia, functional abdominal pain syndrome.

or tetraparesis, and/or hyperreflexia. Although seven patients had some degree of oculomotor dysfunction, only four of these patients showed WD-specific features (i.e., OMM and/or SVGP).

CSF findings in WD

We next performed a comprehensive analysis of CSF parameters and correlated those to clinical presentation. A total of 81 CSF samples from 35 patients were available for analysis (range, 1–12 samples per patient). TW was detected by PCR in 17 of 35 (48.6%) patients (Table 3). In four of 15 (26.7%) patients with repeated PCR tests, the PCR changed from negative to positive during the course of the disease. Overall, routine CSF parameters demonstrated only a slight elevation of protein (median, 506 mg/dl). Accordingly, protein differentiation (performed in 18/35 patients) showed an increased age-adjusted albumin quotient, indicative of blood–brain barrier disruption. None of the patients showed evidence of intrathecal Ig synthesis. CSF cell differentiation was also unremarkable.

We next compared CSF parameters between patients with and without neurological signs and symptoms, and those with classical CNS manifestation with OMM or SVGP (Table 3, right columns). In the group without neurological symptoms, routine CSF parameters were predominantly in the normal range, whereas all patients with OMM or SVGP had at least one abnormal CSF finding. TW DNA was detected in at least one CSF sample by PCR in four of four (100%) patients with OMM or SVGP, nine of 18 patients (50%) patients with other neurological symptoms, and four of 13 (30.8%) patients without any neurological symptoms. Significant differences were observed for protein and lactate levels between neurologically affected and nonaffected patients, as well as for cell counts, protein levels, and albumin quotient for patients with OMM/SVGP versus other neurological symptoms (Figure 1). In summary, there was a significant association between CSF parameters and neurological signs and symptoms, with classical OMM/SVGP showing the most pronounced alterations. Of note, two additional patients without OMM or SVGP, but other oculomotor signs (diplopia), also presented with elevated CSF protein levels.

To further investigate this association, we correlated all relevant clinical, CSF, and imaging parameters (Figure 2). Given the importance of TW PCR and protein levels identified above, patients were clustered according to PCR results and ranked by decreasing protein levels. Strikingly, the presence of oculomotor symptoms including OMM or SVGP, and cognitive dysfunction was restricted to cases with pathological protein levels or positive TW CSF PCR. Similarly, hydrocephalus (studied in detail below) was only observed in patients with high CSF protein levels. Conversely, in the group of patients with a history of ischemic stroke or imaging findings, only four patients had a positive PCR for TW, and five patients had a negative PCR. However, in four of the five cases with negative PCR, the sample had been obtained only after the start of antibiotic therapy, and in the 10th patient with stroke, no PCR of CSF was available.

Prior immunosuppression and IRIS were not associated with the presence of neurological signs or symptoms nor did they significantly correlate with abnormal CSF parameters (data not shown).

In summary, we identified a group of patients characterized by WD-specific neurological symptoms, pathological CSF findings, and risk of developing hydrocephalus, and a second group with other neurological manifestations and frequent ischemic stroke.

Imaging findings in patients with oculomasticatory myorhythmia and/or supranuclear vertical gaze palsy

The patients with OMM and/or SVGP formed a subgroup of four patients, all male, and additionally showing cognitive symptoms and abnormal gait. On MRI, three patients in this group showed infratentorial WD manifestation consisting of periventricular or periaqueductal T2/FLAIR hyperintense lesions with or without contrast enhancement. The fourth patient displayed a progressive leukoencephalopathy, but without infratentorial lesions. Cerebral atrophy was present in two of these patients. A prototypical longitudinal course with an initial presentation with small-step gait disturbance and urinary incontinence due to occlusive hydrocephalus requiring first ventriculostomy, later implantation of a ventriculoperitoneal shunt, and progression to fulminant disease with OMM and SVGP, abnormal gait, and memory impairment is shown as an example for this group (Figure 3). One patient with highly elevated protein, cell count, and lactate levels presented without OMM and/or SVGP but with an unusual tumefactive lesion with ring-like contrast enhancement on MRI suggestive of an abscess (Figure S2). Stereotactic biopsy with microbiological workup demonstrated the presence of TW.

Obstructive hydrocephalus in WD

To further investigate hydrocephalus as a complication of CNS WD, all available MRI scans were centrally reviewed. Three out of 36 patients (8.3%), all with highly elevated CSF protein levels, had clinically manifest hydrocephalus. Of note, hydrocephalus was initially described in four patients, and in three of these, normal-pressure hydrocephalus (NPH) was originally suspected. On central review, imaging criteria of NPH were not met in all three patients. In one patient, the diagnosis of hydrocephalus could not be confirmed after review. In the other patients, hydrocephalus was obstructive due to infratentorial, periaqueductal WD manifestation with consecutive aqueductal stenosis (see, for example, Figure 3e).

Ischemic stroke and Whipple's disease

Finally, we observed an unexpectedly high number of patients with a history or imaging findings of ischemic stroke after the diagnosis of WD (27.8%, 10/36 patients) in this cohort. The median age

TABLE 3 CSF findings by neurological signs and symptoms

	All patients	Patients without neurological symptoms		Patients with neurological symptoms				
				OMM and/or SVGP		OMM and/or SVGP		
				Present	Absent	Present	Absent	
Overall no. of CSF samples, <i>n</i>	81	18	28	35				
No. of patients	36	13	4	19				
Antibiotic treatment at time of lumbar puncture								
Currently untreated	44/81 (54.3%)	15/18 (83.3%)	11/28 (39.3%)	18/35 (51.4%)				
Currently treated	29/81 (35.8%)	1/18 (5.6%)	14/28 (50.0%)	14/35 (40.0%)				
Status unknown	8/81 (9.9%)	2/18 (11.1%)	3/28 (10.7%)	3/35 (8.6%)				
PCR for TW in CSF								
PCR positive	21/70 (30.0%)	4/18 (22.2%)	7/20 (35.0%)	10/32 (31.2%)				
Patients with PCR ever positive	17/35 (48.6%)	4/13 (30.8%)	4/4 (100.0%)	9/18 (50.0%)				
		<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>	<i>n</i>
Basic parameters, samples = <i>n</i>								
Leukocyte count, cells/ μ l	2.00 [1.00–8.00]	60	2.00 [1.00–2.50]	11	6.00 [2.00–9.52]	24	2.00 [1.00–3.00]	25
Patients with leukocyte count \geq 5 cells/ μ l	6/30 (20.0%)		2/10 (20.0%)		2/4 (50.0%)		2/16 (12.5%)	
Total protein, mg/L	506.00 [350.50–783.75]	62	352.00 [302.00–480.75]	10	706.00 [450.25–842.75]	26	484.50 [295.50–665.50]	26
Patients with total protein \geq 450mg/L	15/29 (51.7%)		4/9 (44.4%)		3/4 (75.0%)		8/16 (50.0%)	
Glucose, mg/dl	58.00 [49.50–64.93]	51	56.50 [53.50–61.50]	8	60.00 [50.25–71.75]	22	57.00 [46.00–61.00]	21
Patients with glucose \leq 40mg/dl	4/24 (16.7%)		0/7 (0.0%)		2/4 (50.0%)		2/13 (15.4%)	
Lactate, mg/dl	15.70 [13.70–22.70]	49	13.60 [13.07–14.60]	8	21.90 [15.00–25.25]	23	15.10 [13.50–16.67]	18
Patients with lactate \geq 20mg/dl	4/24 (16.7%)		0/7 (0.0%)		2/4 (50.0%)		2/13 (15.4%)	
CSF protein differentiation, samples = <i>n</i>								
Q_{Alb} , $\times 10^{-3}$	9.81 [6.10–14.60]	29	8.45 [7.30–9.65]	4	14.00 [11.30–16.00]	13	7.05 [5.25–10.11]	12
Patients with elevated age-adjusted Q_{Alb}	9/18 (50.0%)		2/4 (50.0%)		3/4 (75.0%)		4/10 (40.0%)	
Intrathecal IgG Synthesis	0 (0.0%)	28	0 (0.0%)	4	0 (0.0%)	13	0 (0.0%)	11
Intrathecal IgA Synthesis	0 (0.0%)	20	0 (0.0%)	3	0 (0.0%)	11	0 (0.0%)	6
Intrathecal IgM Synthesis	0 (0.0%)	19	0 (0.0%)	3	0 (0.0%)	11	0 (0.0%)	5
CSF specific OCBs	0 (0.0%)	22	0 (0.0%)	2	0 (0.0%)	12	0 (0.0%)	8
CSF cell differentiation, samples = <i>n</i>								
Lymphocytes	68.20 [58.00–75.80]	17	71.60 [64.48–75.30]	4	74.50 [69.27–80.02]	8	58.00 [33.90–59.00]	5
Monocytes	21.40 [15.50–29.40]	17	21.45 [17.47–23.18]	4	20.30 [15.88–24.08]	8	36.70 [15.00–60.70]	5
Neutrophils	3.60 [0.00–6.60]	17	3.60 [3.28–12.90]	4	1.25 [0.00–5.10]	8	5.40 [0.00–27.00]	5
Eosinophils	0.00 [0.00–0.00]	17	0.00 [0.00–0.05]	4	0.00 [0.00–0.00]	8	0.00 [0.00–0.25]	5
Activated lymphocytes	0.00 [0.00–0.00]	17	0.00 [0.00–0.00]	4	0.00 [0.00–0.15]	8	0.00 [0.00–0.00]	5
Plasma cells	0.00 [0.00–0.00]	17	0.00 [0.00–0.00]	4	0.00 [0.00–0.00]	8	0.00 [0.00–0.00]	5

(Continues)

TABLE 3 (Continued)

		<i>n</i>		<i>n</i>		<i>n</i>		<i>n</i>
Macrophages	0.00 [0.00–1.50]	17	0.00 [0.00–0.00]	4	0.15 [0.00–2.79]	8	0.00 [0.00–1.60]	5

Note: Values are given as median with interquartile range or *n*/total with percentage unless otherwise indicated. Values in italics refer to the patient population, values in normal print refer to the CSF sample population.

Abbreviations: CSF, cerebrospinal fluid; Ig, immunoglobulin; OCB, oligoclonal bands; OMM, oculomastatory myorhythmia; PCR, polymerase chain reaction; Q_{Alb} , albumin quotient; SVGP, supranuclear vertical gaze palsy; TW, *Tropheryma whipplei*.

of patients with stroke was older than those without (66 years vs. 52 years, $p = 0.005$). To test whether the frequency of stroke among patients with WD was still disproportionately high, we compared the prevalence of stroke in this study to an age- and sex-matched population comprising 360 individuals of the GEDA cohort, a nationwide representative health information cohort in Germany [29]. Prevalence of stroke was significantly higher in our WD cohort (27.8%) compared to the prevalence of the general population in Germany (3.2%, $p < 0.001$).

We thus investigated possible causes and etiologies, as classified by TOAST [28], of ischemic stroke in WD. First, there was a close temporal relationship between occurrence of ischemic stroke and diagnosis of clinical signs of WD (Table 4). Importantly, in five of the nine patients (55.6%) with available brain imaging data with stroke, infarction in multiple vessel territories suggested a cardioembolic etiology (as exemplified in Figure 4), but atrial fibrillation as the most common risk factor for cardioembolism was not documented for any patient in our cohort. Conversely, definite WD endocarditis was demonstrated in two patients. One of the patients was diagnosed with TW endocarditis based on a positive PCR in blood for TW, and another one showed positive PCR for TW in the explanted aortic valve. Of note, another patient in the cohort without a history of stroke was also diagnosed with TW endocarditis.

Mild to moderate atherosclerosis was described in five patients, but a hemodynamically relevant stenosis was only observed in one case. In this case, MRI revealed a pattern of multifocal proximal intracranial stenoses, and although the diagnosis could not unequivocally be ascertained, an operational diagnosis of putative cerebral vasculitis was established. WD was not diagnosed until 2 years later, so it is not clear whether TW was causative. The patient later developed obstructive hydrocephalus and also experienced IRIS under initial therapy after prior immunosuppression (including methylprednisolone, cyclophosphamide, rituximab, methotrexate, tocilizumab, canakinumab, etanercept, and anakinra).

According to the TOAST classification, out of 10 cases with ischemic stroke, seven were classified as stroke of undetermined

etiology, two as cardioembolic, one as probably cardioembolic, and one as probably due to another etiology.

In summary, we observed a significantly increased prevalence of stroke in patients with WD, many of unknown etiology, and hypothesize that (cryptic) TW endocarditis may be a relevant cause.

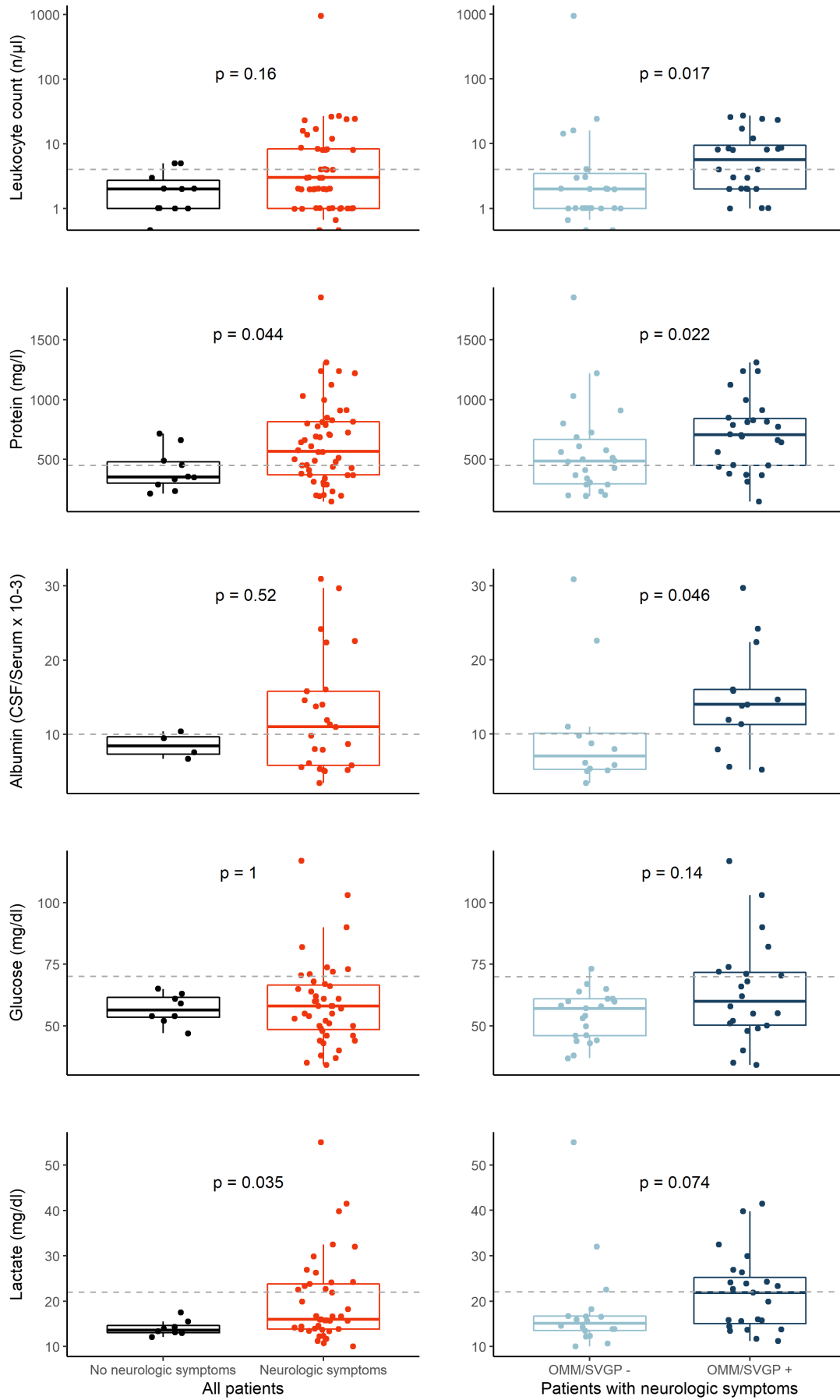
Therapy regimens

Although beyond the scope of this study, patients' individual therapies were also recorded. Treatment recommendations for WD changed during the study period, so patients in this cohort received different therapeutic regimens. Patients were mainly treated with a combination therapy of ceftriaxone followed by cotrimoxazole or doxycycline and hydroxychloroquine, in some cases in combinations with meropenem, minocycline, or interferon γ . A correlation between clinical course and treatment regime could not be observed in this cohort. Similarly, no systematic bias with respect to treatment was observed between patients with and without OMM and/or SVGP, and patients with and without stroke, respectively.

DISCUSSION

This study characterizes the clinical spectrum of CNS involvement in WD and describes corresponding CSF and imaging findings in a large monocentric cohort of patients with WD. Demographically, our cohort is similar to prior studies of WD, with the majority of patients being male and middle aged, and thus appears representative [1, 9]. Prior reports of CSF parameters in patients with WD showed mainly normal results with sometimes slightly elevated protein and cell count levels, and our findings confirm this in a larger monocentric cohort [13, 19, 20]. Compared with recent systematic reviews of published cases with neurological abnormalities, our cohort displays a similar distributed spectrum of symptoms with also most frequent occurrence of cognitive, pyramidal motoric, oculomotor, neuropsychiatric, and hypothalamic dysfunctions [31, 32].

FIGURE 1 CSF findings in patients with and without neurological symptoms with *Tropheryma whipplei* infection. Boxplots showing a comparison of patients with and without neurological symptoms (left column) and a comparison of patients with OMM/SVGP and other neurological symptoms among the group of patients with neurological symptoms (right column). Dotted lines indicate upper reference ranges of CSF parameters. Log scale is used for the y-axis for leukocyte count. Wilcoxon-Mann-Whitney test was used for pairwise comparisons between groups. CSF, cerebrospinal fluid; OMM/SVGP, oculomastatory myorhythmia and/or supranuclear vertical gaze palsy.



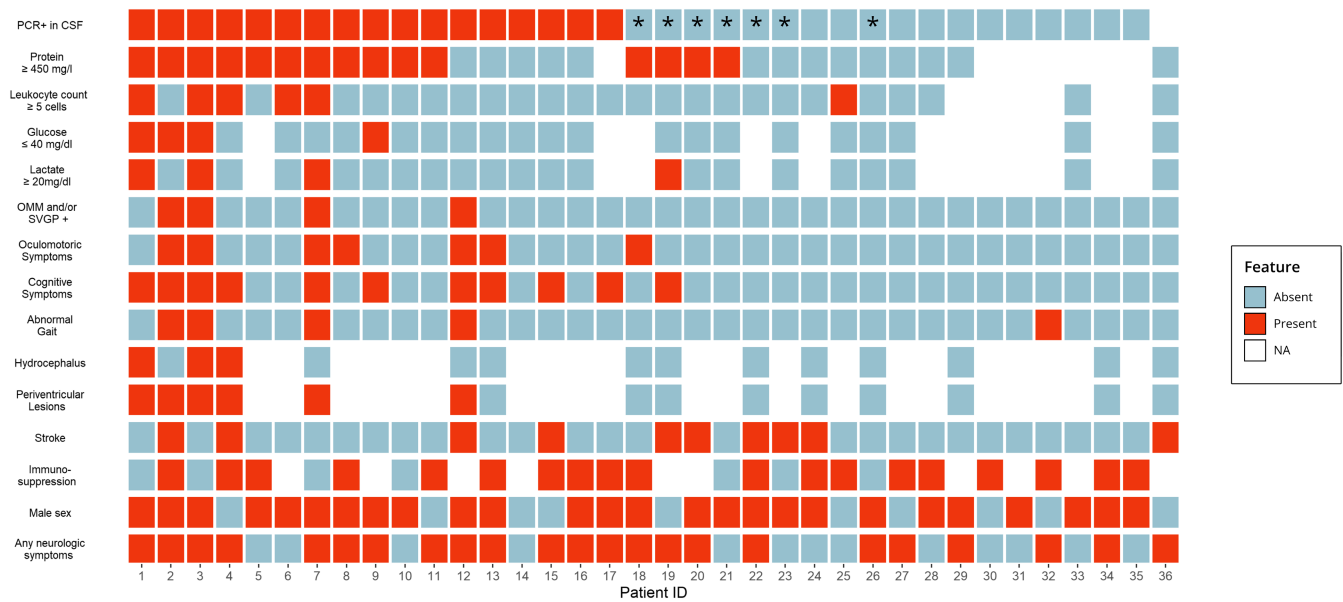


FIGURE 2 Overview of clinical and paraclinical features of patients with *Tropheryma whipplei* infection by PCR and CSF protein findings. Patients were clustered according to PCR results and ranked by decreasing median protein levels. *Negative PCR results were obtained only after the patient received antibiotics. PCR+ in CSF = analysis of positive polymerase chain reaction in the cerebrospinal fluid was positive for *T. whipplei*. CSF, cerebrospinal fluid; ID, identification; OMM and/or SVGP+, oculomasticatory myorhythmia and/or supranuclear vertical gaze palsy; PCR, polymerase chain reaction.

However, correlation with clinical and imaging findings identified several subgroups, likely reflecting several pathomechanisms of CNS involvement in WD: (i) direct parenchymal damage through mostly infratentorial TW infection, which may lead to (ii) obstructive hydrocephalus, and (iii) cerebrovascular events from TW endocarditis.

Parenchymal infection and classical neuro-WD

Patients with distinct symptoms (i.e., OMM or SVGP) displayed frequent CSF abnormalities and invariably tested positive for TW DNA by PCR at least once during the course of the disease, confirming the presence of the pathogen in the CNS. This suggests direct infection with TW (i.e., encephalitis), with a predilection for brainstem structures. In post mortem histological analysis of brain tissue, affected regions included the basal parts of the telencephalon, hypothalamus, thalamus, periaqueductal grey matter, and the quadrigeminal plate [33]. A correlation between histologically and radiologically affected regions is also evident [34].

Importantly, however, neither basic CSF parameters nor positivity of TW PCR in CSF were a definite predictor for OMM, SVGP, or presence of neurological symptoms per se. The presence of the pathogen in the CSF does not necessarily lead to immediate neurological symptoms.

As shown in Table 3, patients with neurological symptoms underwent CSF sampling more frequently while under antibiotic therapy, which is to be expected. Therefore, a bias of the results toward normal CSF parameters and negative PCR cannot be excluded in these groups. In a few patients, positive CSF PCR was only eventually

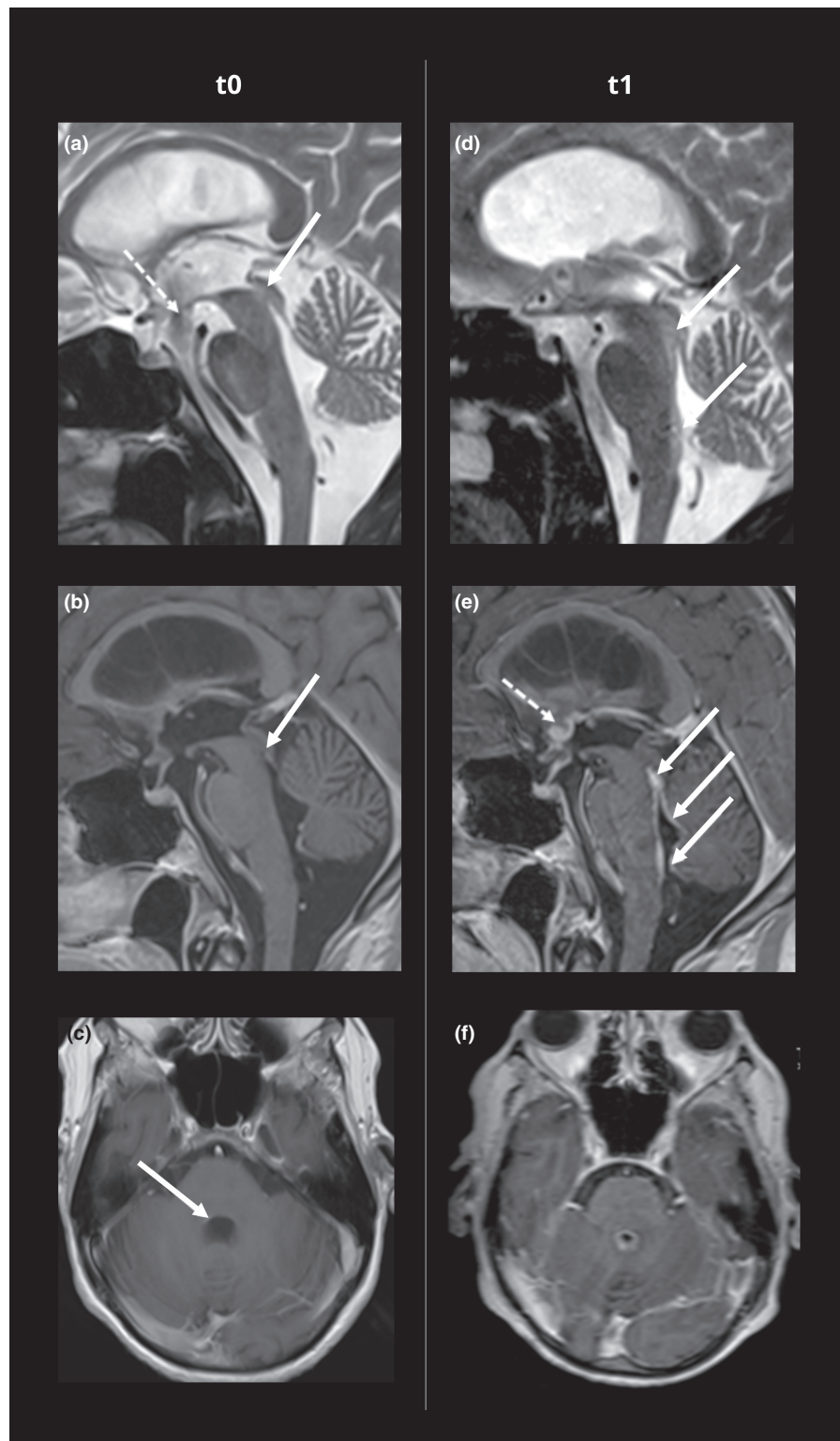
recorded during the course of the disease. This could be due to metachronous CNS infection or because the TW copy number was below the detection level of the PCR. It highlights the importance of repeated PCR testing in the case of suspected CNS involvement [35].

Notably, we found no evidence of intrathecal Ig synthesis in this cohort. Systemic TW-specific immunoreactivity and especially IgG and IgM response are low in patients with WD, which paradoxically may even be used to distinguish patients from asymptomatic carriers who express a stronger immune response [36, 37]. Individual case reports, however, have sporadically reported detection of intrathecal IgA or CSF oligoclonal bands [8, 38]. To our knowledge, TW-specific antibodies have not yet been studied in CSF.

Hydrocephalus

Hydrocephalus manifesting in patients with TW infection has been previously reported [13, 39]. It should be noted that obstruction by aqueductal stenosis was found causative in all three cases in our cohort. Importantly, normal pressure hydrocephalus was initially suspected in three patients but could not be confirmed after central review. Hydrocephalus in WD is thus either directly caused by TW-caused ependymitis or an indirect result of the mass effect of infection of the periaqueductal grey matter, which then leads to aqueduct occlusion [40, 41]. Accordingly, patients should be closely monitored for signs of increased intracranial pressure as it may require ventriculoperitoneal shunt implantation and prolonged continuation of antibiotic treatment. It is noteworthy that the localization of the mass effect is identical or close to the presumed region causative of OMM and SVGP.

FIGURE 3 Case vignette. Longitudinal progress of central nervous system *Tropheryma whipplei* infection over 3 years. Sagittal T2-weighted magnetic resonance imaging (a) in a patient with classical signs of neurological *T. whipplei* infection after surgical third ventriculostomy (time point t_0) due to obstructive hydrocephalus shows aqueductal stenosis secondary to subtle swelling and signal changes of the periaqueductal parenchyma (arrow) and patent ventriculostomy (dotted arrow). (b and c) Contrast-enhanced scans show subtle (sub)ependymal enhancement of the distal aqueduct and the rhomboid fossa. Three years later (time point t_1), sagittal T2 (d) shows progressive swelling of the dorsal midbrain and the rhomboid fossa with obliteration of the aqueduct (arrows). (e and f) Contrast-enhanced scans show progressive (sub)ependymal enhancement of the fourth ventricular linings and the aqueduct (arrows) as well as the lamina terminalis of the third ventricle (dotted arrow).



Association with ischemic stroke

An intriguing finding of this study is the high prevalence of stroke in patients with TW infection. Although patients with stroke were older than WD patients without stroke, prevalence was significantly and more than eightfold higher than in an age- and sex-matched

population control. The occurrence of stroke was associated with positive TW PCR in CSF in only four of 10 patients, so that an etiology independent of CNS infection can be discussed. However, in four patients with negative PCR, the CSF sample was obtained only after the start of treatment, and in one patient, no PCR was performed at all. There was a high rate of cryptogenic stroke and multiterritory

TABLE 4 Characteristics of patients with stroke and *Tropheryma whipplei* infection (n = 10)

Characteristic	Value
Age at stroke, years, median [IQR]	65.50 [59.75–68.75]
Age at diagnosis of WD, years, median [IQR]	66.00 [56.75–69.75]
Female:male (% male)	4:6 (60.0%)
Clinical features	
Signs of endocarditis in TEE	2/6 (33.3%)
Multiterritorial infarction	5/9 (55.6%)
Mild to moderate atherosclerosis ^a	5/6 (83.3%)
Other large vessel pathology ^a	1/6 (16.7%)
Relevant carotid stenosis ^b	0/8 (0%)
Risk factors	
PCR+ for TW in blood or valve	2/2 (100.0%)
Atrial fibrillation	0/6 (0%)
Diabetes mellitus	2/8 (25.0%)
Hypercholesterinemia	5/10 (50.0%)
Hypertension	8/10 (80.0%)
Coronary artery disease	2/8 (25.0%)

Note: Values are given as absolute numbers and percentages (in parentheses) unless otherwise indicated.

Abbreviations: IQR, interquartile range; PCR, polymerase chain reaction; TEE, transesophageal echocardiography; TW, *Tropheryma whipplei*; WD, Whipple's disease.

^aIn extra- and intracranial duplex ultrasound and/or magnetic resonance imaging/computed tomography angiography.

^bIn extracranial duplex ultrasound and/or magnetic resonance imaging/computed tomography angiography.

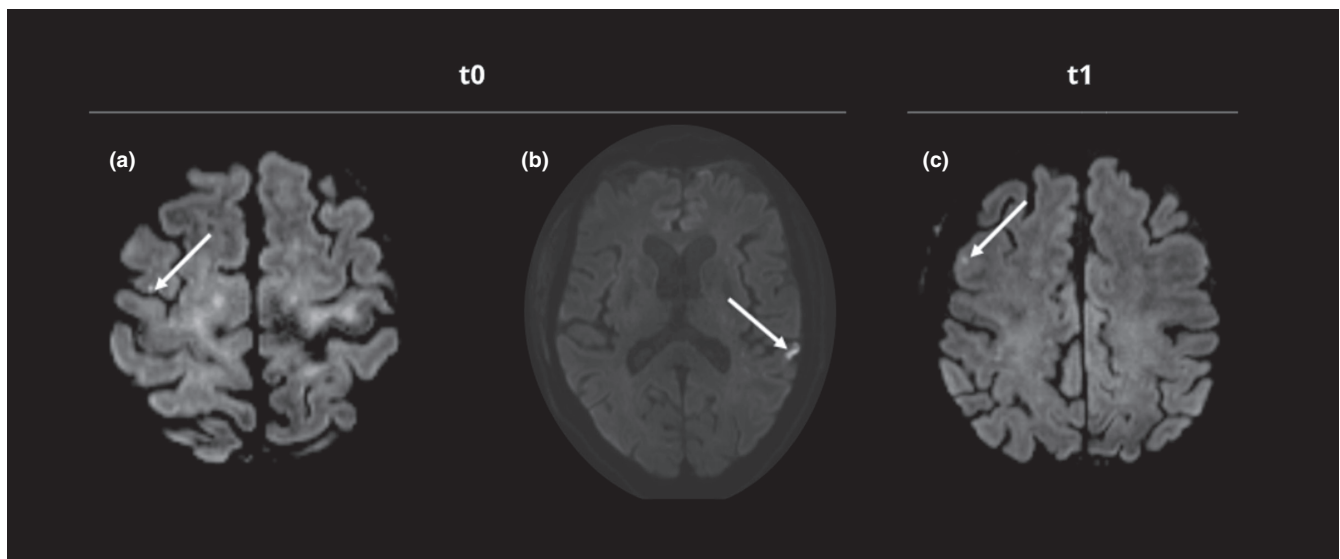


FIGURE 4 Case vignette. Patient with embolic strokes and *Tropheryma whipplei* endocarditis. In a patient with endocarditis with a positive polymerase chain reaction in blood for *T. whipplei*, diffusion weighted imaging (DWI) initially (time point t_0) shows several small foci of acute ischemia bilaterally (a and b), consistent with a cardioembolic origin (arrows). A follow-up scan (c) 2 months later (time point t_1) shows another acute small ischemic focus (arrow).

stroke patterns suggestive of cardioembolism. TW endocarditis, which was confirmed in two cases, may be the most common and plausible pathomechanism. Endocarditis is a well-documented manifestation of WD [42]. Symptoms are often minimal, the modified Duke criteria are typically not met, and PCR from blood has poor sensitivity; therefore, it is challenging to diagnose [42–45]. It is probably

highly underdiagnosed, because a retrospective analysis of excised valves from patients with culture-negative endocarditis showed TW to be a common pathogen in up to 6.3% of cases [44].

Active endocarditis is a strong independent risk factor for developing a cardioembolic stroke [46]. One study reported ischemic stroke in seven out of 28 patients with TW endocarditis (29.2%) [42].

Only one of these patients fulfilled the modified Duke criteria. A CSF sample was obtained from only eight of the 28 patients, and PCR for TW in these was negative in all cases. Our present findings indicate a comparably high rate of strokes in patients with WD overall. Similarly, although not conclusively assessable due to partial lack of initial CSF data, we found no correlation between occurrence of stroke and results of CSF TW PCR.

It is plausible that the increased rate of stroke in our cohort is related to occult endocarditis, even if the relationship cannot be definitively proven retrospectively in most patients. Based on our findings, cardioembolic stroke may be an overlooked mechanism of neurological disease caused by TW, and treating physicians should be aware of it. Additionally, TW endocarditis might be an under-recognized etiology in cryptogenic stroke or suspected cardioembolic stroke without identifiable source of embolism. For these cases, PCR testing of urine might be a valuable tool, because it has a high positive predictive value in initial diagnosis and is easy to obtain [47]. Another emerging noninvasive method in cases of clinical suspicion of systemic infection with TW is 18-fluorodeoxyglucose positron emissitography (18-FDG-PET), which may also be considered for follow-ups in cases of localized infections [48].

Lastly, CNS vasculitis might be another independent etiology of stroke that has been suggested in prior reports of stroke-like syndromes in WD [49–51], although diagnosis of vasculitis could not be confirmed in most cases. However, vasculitis caused by TW has been reported, and it is certainly plausible that it may result in local thromboembolic events [52, 53]. One published report shares similarities with the case of suspected vasculitis reported here; misdiagnosed as rheumatic disease, the patient received extensive immunosuppressive therapy before progressing to CNS vasculitis-like disease with proximal intracranial stenoses and multiple infarctions [54]. Arthralgia as the most common symptom of WD (often preceding the diagnosis by years) might be a red flag for neurologists to consider TW infection.

Limitations

Several limitations apply to our study and are related to sample size and missing data due to its retrospective design. It is therefore of importance to conduct prospective studies to further corroborate the present findings. Especially, establishing the prevalence of TW infection in cryptogenic stroke would be of particular interest. A prospective approach is also needed to further delineate the different pathomechanisms at work in WD and define the resulting phenotypes more precisely.

In conclusion, our results suggest several modes of CNS involvement in WD. Pathomechanisms that should be considered in the assessment of patients with TW infection comprise direct infection of brain parenchyma, hydrocephalus due to aqueduct stenosis, and cardioembolic stroke due to endocarditis. Abnormal CSF findings correspond to a clinical manifestation with specific signs and are probably related to the CNS presence of the pathogen.

In patients with cryptogenic stroke, infection with TW should be considered.

AUTHOR CONTRIBUTIONS

Jasper Mecklenburg: Conceptualization (equal); data curation (lead); formal analysis (equal); visualization (equal); writing – original draft (lead); writing – review and editing (equal). **Verena Moos:** Conceptualization (supporting); data curation (equal); formal analysis (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Annette Moter:** Data curation (equal); writing – original draft (supporting); writing – review and editing (supporting). **Eberhard Siebert:** Data curation (supporting); formal analysis (equal); writing – original draft (supporting). **Alexander Heinrich Nave:** Data curation (supporting); formal analysis (supporting); writing – original draft (supporting). **Thomas Schneider:** Conceptualization (supporting); data curation (equal); writing – original draft (supporting); writing – review and editing (supporting). **Klemens Ruprecht:** Conceptualization (equal); supervision (lead); writing – original draft (equal); writing – review and editing (equal). **Philipp Euskirchen:** Conceptualization (lead); data curation (supporting); formal analysis (equal); supervision (lead); writing – original draft (equal); writing – review and editing (lead).

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data used for the preparation of the tables and figures that is not published in the current study can be shared upon request by

qualified investigators, provided the appropriate institutional review board approvals have been obtained.

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REFERENCES

- Fenollar F, Puechal X, Raoult D. Whipple's disease. *N Engl J Med*. 2007;356(1):55-66. doi:10.1056/NEJMra062477
- El-Abassi R, Soliman MY, Williams F, England JD. Whipple's disease. *J Neurol Sci*. 2017;377:197-206. doi:10.1016/j.jns.2017.01.048
- Biagi F, Balduzzi D, Delvino P, Schiapatti A, Klersy C, Corazza GR. Prevalence of Whipple's disease in North-Western Italy. *Eur J Clin Microbiol Infect Dis*. 2015;34(7):1347-1348. doi:10.1007/s10096-015-2357-2
- Durand DV, Lecomte C, Cathebras P, Rousset H, Godeau P. Whipple disease. Clinical review of 52 cases. The SNFMI research group on Whipple disease. Societe Nationale Francaise de Medecine interne. *Medicine (Baltimore)*. 1997;76(3):170-184. doi:10.1097/00005792-199705000-00003
- Lagier JC, Lepidi H, Raoult D, Fenollar F. Systemic *Tropheryma whippelii*: clinical presentation of 142 patients with infections diagnosed or confirmed in a reference center. *Medicine (Baltimore)*. 2010;89(5):337-345. doi:10.1097/MD.0b013e3181f204a8
- Meunier M, Puechal X, Hoppe E, et al. Rheumatic and musculoskeletal features of Whipple disease: a report of 29 cases. *J Rheumatol*. 2013;40(12):2061-2066. doi:10.3899/jrheum.130328
- Hujoel IA, Johnson DH, Leibold B, et al. *Tropheryma whippelii* infection (Whipple disease) in the USA. *Dig Dis Sci*. 2019;64(1):213-223. doi:10.1007/s10620-018-5033-4
- Panegyres PK, Edis R, Beaman M, Fallon M. Primary Whipple's disease of the brain: characterization of the clinical syndrome and molecular diagnosis. *QJM*. 2006;99(9):609-623. doi:10.1093/qjmed/hcl081
- Marth T, Moos V, Muller C, Biagi F, Schneider T. *Tropheryma whippelii* infection and Whipple's disease. *Lancet Infect Dis*. 2016;16(3):e13-e22. doi:10.1016/S1473-3099(15)00537-X
- Martinetti M, Biagi F, Badulli C, et al. The HLA alleles DRB1*13 and DQB1*06 are associated to Whipple's disease. *Gastroenterology*. 2009;136(7):2289-2294. doi:10.1053/j.gastro.2009.01.051
- Rolain JM, Fenollar F, Raoult D. False positive PCR detection of *Tropheryma whippelii* in the saliva of healthy people. *BMC Microbiol*. 2007;7:48. doi:10.1186/1471-2180-7-48
- Moos V, Kunkel D, Marth T, et al. Reduced peripheral and mucosal *Tropheryma whippelii*-specific Th1 response in patients with Whipple's disease. *J Immunol*. 2006;177(3):2015-2022. doi:10.4049/jimmunol.177.3.2015
- Louis ED, Lynch T, Kaufmann P, Fahn S, Odel J. Diagnostic guidelines in central nervous system Whipple's disease. *Ann Neurol*. 1996;40(4):561-568. doi:10.1002/ana.410400404
- Grotta JC, Pettigrew LC, Schmidt WA, Friedman G, Snatic S. Oculomasticatory myorhythmia. *Ann Neurol*. 1987;22(3):395-396. doi:10.1002/ana.410220325
- Hausser-Hauw C, Rouillet E, Robert R, Marteau R. Oculo-facio-skeletal myorhythmia as a cerebral complication of systemic Whipple's disease. *Mov Disord*. 1988;3(2):179-184. doi:10.1002/mds.870030211
- Averbuch-Heller L, Paulson GW, Daroff RB, Leigh RJ. Whipple's disease mimicking progressive supranuclear palsy: the diagnostic value of eye movement recording. *J Neurol Neurosurg Psychiatry*. 1999;66(4):532-535. doi:10.1136/jnnp.66.4.532
- Silbert SW, Parker E, Horenstein S. Whipple's disease of the central nervous system. *Acta Neuropathol*. 1976;36(1):31-38. doi:10.1007/BF00685145
- Knox DL, Bayless TM, Pittman FE. Neurologic disease in patients with treated Whipple's disease. *Medicine (Baltimore)*. 1976;55(6):467-476. doi:10.1097/00005792-197611000-00003
- Fenollar F, Nicoli F, Paquet C, et al. Progressive dementia associated with ataxia or obesity in patients with *Tropheryma whippelii* encephalitis. *BMC Infect Dis*. 2011;11:171. doi:10.1186/1471-2334-11-171
- Compain C, Sacre K, Puechal X, et al. Central nervous system involvement in Whipple disease: clinical study of 18 patients and long-term follow-up. *Medicine (Baltimore)*. 2013;92(6):324-330. doi:10.1097/MD.0000000000000010
- Wetzstein N, Fenollar F, Buffet S, Moos V, Schneider T, Raoult D. *Tropheryma whippelii* genotypes 1 and 3 Central Europe. *Emerg Infect Dis*. 2013;19(2):341-342. doi:10.3201/eid1902.120709
- Moos V, Feurle GE, Schinnerling K, et al. Immunopathology of immune reconstitution inflammatory syndrome in Whipple's disease. *J Immunol*. 2013;190(5):2354-2361. doi:10.4049/jimmunol.1202171
- Gunther U, Moos V, Offenmuller G, et al. Gastrointestinal diagnosis of classical Whipple disease: clinical, endoscopic, and histopathologic features in 191 patients. *Medicine (Baltimore)*. 2015;94(15):e714. doi:10.1097/MD.0000000000000714
- Feurle GE, Moos V, Schinnerling K, et al. The immune reconstitution inflammatory syndrome in whipple disease: a cohort study. *Ann Intern Med*. 2010;153(11):710-717. doi:10.7326/0003-4819-153-11-201012070-00004
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010
- Spackman KA, Campbell KE, Cote RA. SNOMED RT: a reference terminology for health care. *Proc AMIA Annu Fall Symp*. 1997;640-644.
- Moter A, Schmiedel D, Petrich A, et al. Validation of an rpoB gene PCR assay for detection of *Tropheryma whippelii*: 10 years' experience in a National Reference Laboratory. *J Clin Microbiol*. 2013;51(11):3858-3861. doi:10.1128/JCM.01703-13
- Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of org 10172 in acute stroke treatment. *Stroke*. 1993;24(1):35-41. doi:10.1161/01.str.24.1.35
- Robert Koch-Institut AfEuG. Gesundheit in Deutschland aktuell 2014/2015-EHIS (GEDA 2014/2015-EHIS). *Scientific Use File 1 Version*. doi:10.7797/19-201415-1-1-1
- Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Softw*. 2011;42(8):1-28.
- Manini A, Querzola G, Lovati C, Pantoni L. Rapidly progressive dementia and intractable diarrhea: a teaching case report and a systematic review of cognitive impairment in Whipple's disease. *Neurol Sci*. 2022;43(2):907-926. doi:10.1007/s10072-021-05844-5
- Bally JF, Meneret A, Roze E, Anderson M, Grabli D, Lang AE. Systematic review of movement disorders and oculomotor abnormalities in Whipple's disease. *Mov Disord*. 2018;33(11):1700-1711. doi:10.1002/mds.27419
- Romanul FC, Radvany J, Rosales RK. Whipple's disease confined to the brain: a case studied clinically and pathologically. *J Neurol Neurosurg Psychiatry*. 1977;40(9):901-909. doi:10.1136/jnnp.40.9.901
- Black DF, Aksamit AJ, Morris JM. MR imaging of central nervous system Whipple disease: a 15-year review. *AJNR Am J Neuroradiol*. 2010;31(8):1493-1497. doi:10.3174/ajnr.A2089

35. Mohamed W, Neil E, Kupsy WJ, Juhasz C, Mittal S, Santhakumar S. Isolated intracranial Whipple's disease--report of a rare case and review of the literature. *J Neurol Sci.* 2011;308(1-2):1-8. doi:10.1016/j.jns.2011.05.029
36. Fenollar F, Amphoux B, Raoult D. A paradoxical *Tropheryma whipplei* western blot differentiates patients with whipple disease from asymptomatic carriers. *Clin Infect Dis.* 2009;49(5):717-723. doi:10.1086/604717
37. Bonhomme CJ, Renesto P, Nandi S, Lynn AM, Raoult D. Serological microarray for a paradoxical diagnostic of Whipple's disease. *Eur J Clin Microbiol Infect Dis.* 2008;27(10):959-968. doi:10.1007/s10096-008-0528-0
38. Carella F, Valla P, Bernardi G, Parente F, Costa A, Lodrini S. Cerebral Whipple's disease: clinical and cerebrospinal fluid findings. *Ital J Neurol Sci.* 1998;19(2):101-105. doi:10.1007/BF02427566
39. Seneca V, Imperato A, Colella G, Cioffi V, Mariniello G, Gangemi M. Recurrent acute obstructive hydrocephalus as clinical onset of cerebral Whipple's disease. *Clin Neurol Neurosurg.* 2010;112(8):717-721. doi:10.1016/j.clineuro.2010.04.021
40. Chiang F, Verde AR, Sossa DE, Sossa DG, Castillo M. Aqueductal stenosis secondary to Whipple's disease. *JBR-BTR.* 2013;96(6):395. doi:10.5334/jbr-btr.527
41. Leinonen V, Vanninen R, Rauramaa T. Cerebrospinal fluid circulation and hydrocephalus. *Handb Clin Neurol.* 2017;145:39-50. doi:10.1016/B978-0-12-802395-2.00005-5
42. Fenollar F, Celard M, Lagier JC, Lepidi H, Fournier PE, Raoult D. *Tropheryma whipplei* endocarditis. *Emerg Infect Dis.* 2013;19(11):1721-1730. doi:10.3201/eid1911.121356
43. Gubler JG, Kuster M, Dutly F, et al. Whipple endocarditis without overt gastrointestinal disease: report of four cases. *Ann Intern Med.* 1999;131(2):112-116. doi:10.7326/0003-4819-131-2-199907200-00007
44. Geissdorfer W, Moos V, Moter A, et al. High frequency of *Tropheryma whipplei* in culture-negative endocarditis. *J Clin Microbiol.* 2012;50(2):216-222. doi:10.1128/JCM.05531-11
45. Thornton CS, Wang Y, Koebel M, et al. Another Whipple's triad? Pericardial, myocardial and valvular disease in an unusual case presentation from a Canadian perspective. *BMC Cardiovasc Disord.* 2019;19(1):312. doi:10.1186/s12872-019-1257-2
46. Merkle AE, Chu SY, Lerario MP, Navi BB, Kamel H. Temporal relationship between infective endocarditis and stroke. *Neurology.* 2015;85(6):512-516. doi:10.1212/WNL.0000000000001835
47. Moter A, Janneck M, Wolters M, et al. Potential role for urine polymerase chain reaction in the diagnosis of Whipple's disease. *Clin Infect Dis.* 2019;68(7):1089-1097. doi:10.1093/cid/ciy664
48. Lagier JC, Camilleri S, Raoult D. Classic Whipple's disease diagnosed by (18)F-fluorodeoxyglucose PET. *Lancet Infect Dis.* 2016;16(1):130. doi:10.1016/S1473-3099(15)00503-4
49. Famularo G, Minisola G, De Simone C. A patient with cerebral Whipple's disease and a stroke-like syndrome. *Scand J Gastroenterol.* 2005;40(5):607-609. doi:10.1080/00365520510015494
50. Peters G, du Plessis DG, Humphrey PR. Cerebral Whipple's disease with a stroke-like presentation and cerebrovascular pathology. *J Neurol Neurosurg Psychiatry.* 2002;73(3):336-339. doi:10.1136/jnnp.73.3.336
51. El Helou J, Saliba G, Kolev I, Pierrot-Deseilligny C. Neuro-Whipple confirmed five years after a presumptive diagnosis of a primitive CNS vasculitis. *J Neurol.* 2008;255(6):925-926. doi:10.1007/s00415-008-0597-0
52. Lo Monaco A, Govoni M, Zelante A, et al. Whipple disease: unusual presentation of a protean and sometimes confusing disease. *Semin Arthritis Rheum.* 2009;38(5):403-406. doi:10.1016/j.semarthrit.2008.03.007
53. Al-Hamoudi W, Habbab F, Nudo C, Nahal A, Flegel K. Eosinophilic vasculitis: a rare presentation of Whipple's disease. *Can J Gastroenterol.* 2007;21(3):189-191. doi:10.1155/2007/326174
54. Giollo A, Zivelonghi C, Cardellini D, et al. THU0591 central nervous system vasculitis in WHIPPLE disease: a Case report. *Ann Rheum Dis.* 2020;79(Suppl 1):537-538. doi:10.1136/annrheumdis-2020-eular.4985

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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