USEFULNESS OF POLYMERASE CHAIN REACTION FOR DIAGNOSING WHIPPLE'S DISEASE IN RHEUMATOLOGY

SAT 0561

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Background

Whipple's disease should be considered in patients with

Recurrent episodes of unexplained seronegative arthritis in the large limb
Chronic diarrhoea, persistent fever, unexplained neurological signs, uveitis
Blood-culture- negative endocarditis, and epithelioid granuloma

Laboratory tests may show

Malabsorption, eosinophilia,
erythrocyte sedimentation rate and C-reactive protein elevation,
anaemia, thrombocytosis, and lymphopenia.

None of these findings is specific.

Our aim was to determine when patients should undergo *T. whipplei* PCR testing

Methods

Retrospective observational study done in five hospitals in western France

Clinical and radiological signs that prompted *T. whipplei* PCR testing
Between 2010 and 2014

We evaluated

Proportion of patients diagnosed with Whipple's disease,
Number of tests performed in each centre
Number of diagnoses according to the number of tests
Patterns of Whipple's disease,
Treatments used.

Patients were divided

CWD: Classic Whipple's disease (duodenal biopsy positive by PAS staining or T. whipplei immunohistochemistry, or as stool and saliva positive by PCR plus skin biopsy positive, or as blood positive by PCR);

FWD: Focal Whipple's disease (joint fluid positive by PCR but duodenal biopsy negative by PAS staining and immunohistochemistry);

CTWAA: Chronic T. whipplei-associated arthritis (duodenal biopsy, stool, or saliva positive by PCR but duodenal biopsy and joint fluid negative).

Figure 1: Number of patients with at least one PCR test (grey), a diagnosis of Whipple's disease (white) according to population (black)

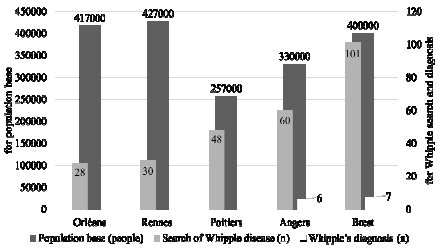


Table 1: Description of Whipple's disease

CASE	PAS on duodenal biopsy	PCR on stool	PCR on saliva	PCR on duodenal biopsy	PCR on joint fluid	PCR on blood	Pattern
			BREST				
1	negative	**positive**	**positive**	negative	not made	not made	CTWAA
2	negative	**positive**	**positive**	negative	not made	negative	CTWAA
3	negative	**positive**	**positive**	negative	**positive**	negative	FWD
4	**positive**	**positive**	**positive**	**positive**	not made	negative	CWD
5	negative	negative	negative	negative	**positive**	negative	FWD
6	negative	**positive**	negative	negative	not made	negative	CTWAA
7	negative	**positive**	**positive**	**positive**	not made	negative	CTWAA
			ANGERS				
8	negative	**positive**	**positive**	**positive**	not made	negative	CWD
9	**positive**	**positive**	**positive**	**positive**	not made	**positive**	CWD
10	negative	**positive**	**positive**	not made	not made	negative	CTWAA
11	negative	**positive**	**positive**	not made	not made	negative	CTWAA
12	negative	**positive**	negative	negative	negative	negative	CTWAA
13	negative	**positive**	**positive**	**positive**	negative	negative	CWD

Figure 2: Examples of Whipple's diseases mimicking ankylosing spondylitis with multiple discitis (1a) or rheumatoid arthritis (1b)

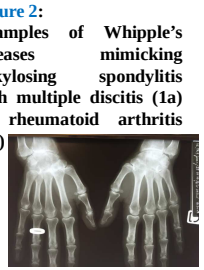
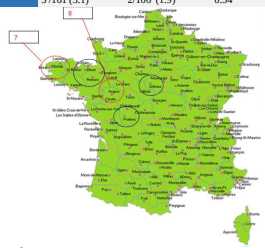


Table 1: Description of Whipple's disease

Clinical signs	Brest and Angers: 13 diagnoses 161 tests	Orléans, Poitiers, and Rennes: no diagnoses 106 tests	*p* value univariate	*p* value multivariate
Age	53.42 (14.75)	49.30 (15.80)	**0.05**	**0.029**
Male gender	82/161 (51.0)	46/106 (43.4)	0.23	0.11
Arthralgia	144/161 (89.4)	95/106 (89.6)	0.96	
Arthritis	120/161 (74.5)	53/106 (50.0)	**<0.001**	**<0.001**
Radiological erosion	65/161 (40.4)	43/106 (40.6)	0.97	
Inflammatory low back pain	49/161 (30.4)	36/106 (34.0)	0.54	
Constitutional symptoms	57/161 (35.4)	54/105 (51.4)	**0.01**	**0.016**
Fever	22/160 (13.7)	31/106 (29.2)	**0.002**	**0.001**
Diarrhoea	38/161 (23.6)	32/103 (31.1)	0.18	0.103
Lymphadenopathy	5/161 (3.1)	9/101 (8.9)	**0.04**	0.066
Uveitis	5/161 (3.1)	2/91 (2.2)	0.67	
Neurological signs	4/161 (2.5)	7/101 (6.9)	0.08	0.066
Pleural effusion	0/160 (0)	2/100 (2)	0.07	0.066
Endocarditis	0/161 (0)	1/106 (0.9)	0.22	0.195
Tests performed in centers	134/161 (83.2)	41/106 (38.7)	**<0.0001**	
Stool PCR				
Saliva PCR	145/161 (90.1)	65/106 (61.3)	**<0.0001**	
Joint fluid PCR	41/161 (25.5)	9/106 (8.5)	**0.0005**	
Duodenal biopsy	46/161 (28.6)	30/106 (28.3)	0.96	
Urine PCR	57/161 (35.4)	12/106 (11.3)	**<0.0001**	
Blood PCR	93/161 (57.8)	71/106 (67.0)	0.13	
CSF PCR	5/161 (3.1)	2/106 (1.9)	0.54	



Conclusion: Males aged 40-75 years with unexplained intermittent seronegative peripheral polyarthritis, including those without constitutional symptoms, should have *T. whipplei* PCR tests on saliva, stool and, if possible, joint fluid.

Table 2: Comparison tested patients with and without a diagnosis of Whipple's disease

	Patients with Whipple disease, n=13	Patient without Whipple disease, n=254	p value univariate	p value multivariate
Age, years (SD)	60.5 (11.1)	51.3 (15.35)	0.03	0.094
Male gender	11/13 (84.6)	117/254 (46.1)	0.007	0.019
Arthralgia	13/13 (100)	226/254 (89)	0.21	0.998
Arthritis	13/13 (100)	160/254 (63)	0.01	0.996
Inflammatory low back pain	3/13 (23.1)	82/254 (33.3)	0.49	
Constitutional symptoms	6/13 (46.1)	105/253 (41.5)	0.74	
Fever	3/13 (23.1)	50/253 (19.8)	0.72	
Diarrhoea	3/13 (23.1)	67/251 (26.7)	0.77	
Lymphadenopathy	0/13 (0)	14/249 (5.6)	0.38	
Uveitis	0/13 (0)	7/239 (2.9)	0.53	
Neurological signs	0/13 (0)	11/249 (4.4)	0.44	
Endocarditis	0/13 (0)	1/254 (0.4)	0.75	
Pleural effusion	0/13 (0)	2/247 (0.8)	0.74	
Radiological erosions	6/13 (4.6)	102/254 (40.2)	0.67	
Stool PCR positive	12/13 (92.3)	8/162 (4.9)	<0.001	
Saliva PCR positive	10/13 (77.0)	3/197 (1.5)	<0.001	
Joint fluid PCR positive	2/4 (50.0)	1/46 (2.2)	<0.001	
Duodenal biopsy PCR positive	4/9 (44.4)	0/67 (0)	<0.001	
Urine PCR positive	1/7 (14.3)	0/62 (0)	0.003	
Blood PCR positive	1/12 (8.3)	0/152 (0)	<0.001	
CSF PCR positive	0/3 (0)	0/4 (0)	-	

Table 3: Diagnostic value of PCR

	TP	FP	FN	TN	Se	Sp	PPV	NPV
Male gender	11	117	2	137	84.6	53.9	8.6	98.6
Arthralgia	13	226	0	28	100	11.0	5.4	100
Arthritis	13	160	0	94	100	37.0	7.5	100
Inflammatory low back pain	3	80	10	172	23.1	67.7	3.5	94.5
Constitutional symptoms	6	105	7	148	46.1	58.5	5.4	95.5
Fever	3	50	10	203	23.1	80.2	5.7	95.3
Diarrhoea	3	67	10	184	23.1	73.3	4.3	94.8
Lymphadenopathy	0	14	13	137	0	94.4	0	94.8
Radiological erosions	6	102	7	152	25.0	59.8	5.6	95.6
Male gender, age 40-75 and arthritis	10	56	3	198	76.9	77.9	15.2	98.5

Results

At least one PCR test was performed in each of 267 patients. Main signs are listed table 2.

The main samples tested and the more frequently positive tests in the centres with diagnoses of Whipple's disease were saliva and stool.

In the centres with no diagnoses of Whipple's disease, arthritis was less common, whereas constitutional symptoms, fever, and lymphadenopathy were more common.

11 patients with Whipple's disease had CRP elevation.

The annual incidence ranged across centres from 0 to 3.6/100000 inhabitants.

The group with Whipple's disease had a higher proportion of males, older age, and greater frequency of arthritis.