

## BRAZILIAN STUDIES ON TROPICAL SPASTIC PARAPARESIS

### A META-ANALYSIS

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**SUMMARY** - Tropical spastic paraparesis (TSP) is a chronic progressive myelopathy and in most of the cases has a retroviral (HTLV-1) etiology, when it is denominated HTLV-1 associated-mielopathy (HAM/TSP). Around 433 cases of TSP have been described in Northeast and Southeast Brazil. Among these cases, 157 (36.2%) are HTLV-1 positive and 276 (63.7%) are negative. Their mean age is 43.8 years with a slight predominance of females and mulattoes, although white patients are also numerous. Clinically all patients exhibit a spastic paraparesis with variable sphincter and sensory disturbance. Pain and autonomic symptoms seem to be expressive in the HTLV-1 positive HAM/TSP Brazilian patients.

**KEY WORDS:** tropical spastic paraparesis, HTLV-1, Brazil.

#### Estudos brasileiros sobre paraparesia espástica tropical: meta-análise

**RESUMO** - A paraparesia espástica tropical (PET) é uma mielopatia crônica progressiva e em muitos casos tem etiologia retroviral (HTLV-1), quando é denominada mielopatia associada ao HTLV-1 (MAH/PET). Cerca de 433 casos de PET têm sido descritos no Nordeste e Sudeste do Brasil, dos quais 157 (36,2%) são HTLV-1 positivos e 276 (63,7%) são negativos. A média de idade dos pacientes é de 43,8 anos. Ocorre discreto predomínio de mulheres e mulatos, embora haja numerosos pacientes brancos. Clinicamente todos os pacientes exibem uma paraparesia espástica com variável distúrbio sensitivo e esfinteriano. Dor e sintomas autonômicos parecem expressivos nos pacientes brasileiros com MAH/PET HTLV-1 positivos.

**PALAVRAS-CHAVE:** paraparesia espástica tropical, HTLV-1, Brasil.

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Tropical spastic paraparesis (TSP) is a chronic progressive myelopathy predominant in the tropics and Japan. In the tropical areas it has been described in Africa, India, Seychelles Islands, the Caribbean and Latin America<sup>14,28</sup>. In South America it was described for the first time by Zaninovic in 1981 in Colombia (Tumaco)<sup>32</sup> where a cluster of such patients exists. In Brazil, the first clinical cases were published in 1989<sup>19</sup> and since then Brazilian neurologists have enriched and increased the reports on it<sup>1-13,15-19,21-27,29-31</sup>.

This paper aims to do a perusal of the literature on TSP in Brazil and to point out the characteristics of the Brazilian TSP studies. Moreover it intends to analyze critically these papers in order to stimulate further studies on TSP in Brazil.

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## METHODOLOGY

For this analysis we collected and analyzed the papers published by Brazilian authors in national and international journals. Despite exhaustive search for these papers it may happen, by chance, that some have not been included and for this we apologize their authors in advance.

## RESULTS

Up to now around 29 papers have been published. They concern clinical, demographic, serological and therapeutical features of TSP (Table 1, 2, 3, 4) as well as cerebrospinal fluid (CSF) characteristics of the patients (Table 5). Some papers deal with several aspects of HTLV and neurology, familial studies of TSP, neuroimaging aspects and systemic manifestations of retroviral (HTLV-1) infection (Table 1). In the Brazilian papers around 433 cases of TSP have been reported and of them 157 are HTLV-1 positive and 276 negative (Table 2). Among the TSP cases, their mean age was 43.8, with a slight predominance of females (149 women and 140 men) and 111 were white, 134 mulattoes and 27 blacks (Table 3). These patients have been reported from only two regions of Brazil: Northeast (Ceará, Pernambuco, Bahia) and Southeast (São Paulo and Rio de Janeiro) (Table 1).

## COMMENTS

The relation of HTLV-1 to many of TSP patients in some regions of Brazil supports the notion of the presence and endemicity of this virus in this country. However, the serological tests for HTLV-1 used in the different Brazilian series do not include, in all studies, complete screening and confirmatory tests (Table 2)<sup>9,15,17,21,22,24,27,29,30</sup>.

*Table 1. Brazilian TSP studies: authors, objectives and geographical origin of patients.*

Authors	Year	Objectives	Origin
De Castro-Costa et al (19)	1989	Clinico-demographic	Ceará
Castro et al (15)	1989	Clinico-serological and CSF*	São Paulo
Spina-França et al (29)	1990	CSF and Serology	São Paulo
De Castro-Costa et al (17)	1991	Clinico-serological	Ceará
Takayanagui et al (30)	1991	Clinico-serological and CSF	São Paulo
Moreno Carvalho et al (27)	1992	Clinico-serological and CSF	Bahia
Meireles et al (24)	1992	Clinico-serological and CSF	Bahia
Melo et al (25)	1992	TSP treatment (Danazol)	Bahia
Araújo et al (1-7,12,13)	1992	HTLV and neurology	Rio de Janeiro
Araújo et al (11)	1992	Clinico-serological	Rio de Janeiro
Araújo et al (10)	1993	Clinico-demographic	Rio de Janeiro
Araújo et al (9)	1993	Clinico-serological and CSF	Rio de Janeiro
Araújo et al (8)	1993	TSP Treatment (methylprednisolone)	Rio de Janeiro
Cavalcanti et al (16)	1993	TSP familial study	Rio de Janeiro
Melo et al (26)	1993	TSP and MRI**	Bahia
Mattos et al (23)	1993	Systemic manifestations in TSP	Bahia
Yasuda N (31)	1993	Epidemiological analysis	São Paulo
Guedes et al (21)	1993	Clinico-serological and CSF	Pernambuco
Andrade-Filho et al	in press	Clinico-serological and CSF	Bahia
De Castro-Costa et al (18)	1993	HTLV and neurology	Ceará
De Castro-Costa et al	in preparation	Clinico-seroepidemiological	Ceará
De Castro-Costa et al	in press	Historical analysis of TSP	Ceará
Lessa et al (22)	1993 (dec.)	Analytical-serological and CSF	Bahia

\*CSF, cerebrospinal fluid; \*\*MRI, magnetic resonance imaging.

Table 2. Brazilian TSP studies: serological analysis of TSP patients.

Authors	Total of TSP Patients	HTLV-1		Anti-HTLV-1 used Test			Anti-HIV Test	
		Pos %	Neg %	PA	ELISA	Western Blot IFAT		
De Castro-Costa et al (17,19*)	31	13	18	+	+	+	+	Neg.
Castro et al (15)	16	6	10	NP	+	+	NP	Neg.
Spina-França et al (29)	56	31	25	+	NP	NP	NP	Neg.
Takayanagui et al (30)	14	5	9	+	+	NP	NP	NP
Moreno-Carvalho et al (27)	28	16	12	NP	+	+	NP	?
Meireles et al (24)	43	9	34	NP	+	+	NP	1 posit.
Araújo et al (9)	60	34	26	NP	NP	+	+	Neg.
Guedes et al (21)	95	14	81	NP	+	NP	NP	NP
Andrade-Filho et al (**)	62	17	45	NP	+	+	NP	NP
Lessa et al (22)	28	12	16	NP	+	+	NP	Neg.
Total	433	157	276					
		36.2	63.7					

NP, not performed; \* in preparation; \*\* in press; PA, particle agglutination; IFAT, immunofluorescence.

Since 1989 an increasing interest has grown on TSP in Brazil and the papers are mainly concerned with its clinical and serological features.

The clinical descriptions lie mostly on the classical signs of the syndrome, namely the pyramidal signs present in all cases and the variable presence of sphincter and sensory disturbances (Table 4)<sup>9,17,19,21,24,30</sup>. One of the gaps in this clinical analysis is the definition of the initial symptoms and the progression of the full picture. Only some papers give information of the mean evolution of the patients<sup>9,17,19,21</sup>. The studies on TSP in Brazil and elsewhere have not depicted the natural history of the condition and are only limited to notification of cases in a temporal segment of their evolution. Nobody has yet followed up the patients longitudinally and this opens an interesting aspect in this research. Moreover, as far as the number of cases is concerned, some authors have a trend to repeat their series in different papers so that we cannot know what the exact number of patients they have. It is therefore necessary that the authors make explicit who is who in each other paper. In some papers there is also an interest on other neurological and systemic symptoms<sup>9,23</sup>. This may contribute to the understanding of the clinical spectrum of retroviral-bound conditions. This may be a promising step, but we should be aware to define exactly what is TSP clinically to prevent misdiagnosis of similar conditions.

From the demographic point of view, we call attention to the number of HTLV-1 negative TSP cases which reaches about 63.7% of the obscure myelopathies (Table 2). Despite some series with predominance of negroes and mulattoes, other series also report an important number of white patients<sup>9,17,29</sup>. In many papers of Brazilian authors there is a lack of information on blood transfusion, sexually transmitted diseases, intravenous drug addiction, breast-feeding and homosexuality (Table 3). Another gap resides on the territorial extent of TSP surveys in Brazil. The studies have been carried out in only some areas of Brazil and no data are so far available from South, Center and North Brazil. Only one paper has performed a familial study of TSP<sup>16</sup> and this represents a step for understanding of HTLV-1 transmission and spreading in Brazil.

Table 3. Brazilian TSP patients: demographic characteristics.

Authors	HTLV-1 positive and negative patients												History of					
	Total of patients		Age (mean)				Sex		Race				Blood Transf. STD					
	Pos.	Neg.	Pos.	Neg.	F	M	W	Mul	BI	Pos.	Neg.	Pos.	Neg.	feed	Sex.	IVDA		
De Castro-Costa et al (17,19*)	31	39.9	42.8	10	12	3	6	5	1	8	17	-	-	-	-	1	-	
Castro et al (15)	16	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Spina-França et al (29)	56	46.1	42.2	13	8	18	17	22	18	9	7	-	-	-	-	-	-	
Takayanagui et al (30)	14	48.0	-	2	-	3	-	4	-	1	-	-	-	-	-	-	-	
Moreno-Carvalho et al (27)	28	43.5	-	13	1	3	11	4	-	11	-	1	-	-	-	-	-	
Meireles et al (24)	43	18/56	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	
Araújo et al (9)	60	45	45.4	17	9	17	17	17	14	5	7	12	5	3	-	5	23	
Guedes et al (21)	95	44.7	-	9	-	5	-	6	-	7	-	1	-	2	-	1	-	
Andrade-Filho et al (**)	62	44.1	43.1	16	20	1	25	4	16	10	24	3	5	3	-	-	-	
Lessa et al (22)	28	44.6	-	14	14	14	14	-	-	28	-	-	-	1	-	1	-	
Mean / Total		(43.8)		(149)		(140)		(111)		(134)		(27)		(10)	(0)	(6)	(26)	(5)

- not show; \* in press; \*\* in preparation; ( ) both positive and negative cases; SID, sexually transmitted diseases; IVDA, intravenous drug addiction.

Table 4. Brazilian TSP studies: clinical characteristics of TSP patients.

Authors	HTLV-1		Evol				Symptoms at onset						Symptoms and signs					
	Total of patients	Pos. Neg.	Year	motor		auton.		pain		Pyram.	Sphinct.		Sensory		Others			
				Pos.	Neg.	Pos.	Neg.	Pos.	Neg.		Pos.	Neg.	Pos.	Neg.				
De Castro-Costa et al (17,19*)	31	13	18	4.0	6	15	1	2	6	1	13	18	11	17	4	4	3	4
Castro et al (15)	16	6	10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Spina-França et al (29)	56	31	25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Takayanagi et al (30)	14	5	9	-	-	-	-	-	-	-	5	9	-	-	-	-	-	-
Moreno-Carvalho et al (27)	28	16	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Meireles et al (24)	43	9	34	-	-	-	-	-	-	-	9	34	9	34	0	0	-	-
Araújo et al (9)	60	34	26	5.5	21	11	6	0	7	7	34	26	32	16	15	7	7	7
Guedes et al (21)	95	14	81	7.0	-	-	-	-	-	-	14	-	9	-	7	-	-	-
Andrade-Filho et al (**)	62	17	45	-	-	-	-	-	-	-	17	45	17	45	13	77	-	-
Mean / Total	433	167	276	5.5	27	26	7	2	13	8	92	132	78	112	39	88	10	11

- not shown; \* in preparation; \*\* in press.

Table 5. Brazilian TSP studies: CSF characteristics of TSP patients.

Authors	Pleocytosis HTLV-1						CSF findings					
	HTLV-1		Hyperproteinorachia HTLV-1		Increased IgG HTLV-1		HTLV-1		HTLV-1		HTLV-1	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Castro et al (15)	Mild	NR	Discrete	NR	Discrete	NR	Discrete	NR	Discrete	NR	Discrete	NR
Spina-França et al (29)	Discrete	Normal	Moderate	Normal	Moderate	Normal	Discrete to mod.	Normal	Discrete to mod.	Normal	Discrete to mod.	Normal
Takayanagi et al (30)	Mild	NR	Discrete	NR	Discrete	NR	Moderate	NR	Moderate	NR	Moderate	NR
Moreno-Carvalho et al (27)	Discrete to mod.	Normal	Discrete to mod.	Normal	Discrete to mod.	Idem	Discrete to mod.	Idem	Discrete to mod.	Normal	Discrete to mod.	Normal
Meireles et al (24)	Discrete	NR	Discrete	NR	Discrete	NR	Discrete	NR	Discrete	NR	Discrete	NR
Araújo et al (9)	Discrete	Discrete	Mild	Discrete	Discrete	Normal	Moderate	Normal	Moderate	Normal	Moderate	Normal
Andrade-Filho et al (*)	Mild	NR	Mild	NR	Mild	NR	Mild	NR	Moderate	NR	Mild	NR
Guedes et al (21)	Mild	NR	Mild	NR	Mild	NR	Mild	NR	Mild	NR	Mild	NR
Lessa et al (22)	Mild	NR	Mild	NR	Mild	NR	Mild	NR	Mild	NR	Mild	NR

NR, not reported; \* in press.

A not-yet defined point is the etiological final definition of TSP. Since Gessain's report in 1985<sup>20</sup> on HTLV-1 related TSP there is an imperative posture to relate strictly this syndrome to HTLV-1 and all other TSP cases without this connexion are thought to be doubtful. This had led to misdiagnosis of other myelopathic conditions<sup>31</sup>. The retroviral etiology is nevertheless a very important clinical and epidemiological finding in TSP, because it is the first true and proven etiology for one of the obscure tropical myelopathies. However this should not block further etiological research for the negative cases.

The CSF profile of TSP patients has also been presented in some Brazilian series (Table 5). Some papers have done it in a systematized way<sup>9,11,22,29</sup> and shown slight to moderate changes in cells, glucose, protein values and electrophoretic picture. Less expressive changes in HTLV-1 negative TSP patients help differentiating them, and are probably due to timing of viral activity<sup>9,29</sup>.

Very few papers<sup>8,25</sup> are bound to therapeutical approaches of TSP patients. Therapeutical assays have produced unsuccessful results with prednisolone and danazol and this still represents a challenging domain in this clinical entity.

As we have seen, many gaps exist in the different papers of Brazilian authors. One of the ways we may overcome such difficulties is the definition and use of a common clinical and demographic protocol such as this proposed by Dr. Abelardo Araújo from Fiocruz (personal communication). The use of this protocol in a multicentric national collaborative study will make possible a definition of the profile of the Brazilian TSP patients. Moreover analytical studies such as the one carried out recently in Salvador<sup>22</sup>, may also bring a contribution to define the association between myelopathy and HTLV-1.

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