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DISCREPANCY, COINCIDENCE OR EVIDENCE IN CHRONIC IDIOPATHIC SPASTIC PARAPARESIS THROUGHOUT THE WORLD

A META-ANALYSIS ON 2811 PATIENTS

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ABSTRACT - HTLV-I has been associated with a chronic idiopatic spastic paraparesis (CHISPA) in man; however, a complete understanding of this association is still debated. We selected the most comprehensible papers on this topic between 1985 and 1996, and found that 1261 out of 2811 patients (44.9%) reported, throughout the world, were HTLV-I positive. The mean age was 39.5 years and there was a female predominance of 1.9:1. These results do not exclude the causality of HTLV-I as a germen associated to CHISPA; however, other causes (e.g., toxic, immunosuppressors) must be considered as participating in the multistep neurodegeneration observed in CHISPA throughout the world.

KEY WORDS: HTLV-I, spastic paraparesis, meta-analysis, retrovirus, environmental cofactors.

Discrepância, coincidência ou evidência em paraparesia espástica idiopática crônica no mundo: uma meta-análise de 2811 pacientes

RESUMO - O retrovirus HTLV-1 tem sido associado a paraparesia espástica idiopática crônica (PEIC) no homem; contudo uma compreensão completa dessa associação é motivo de debate. Selecionamos os estudos mundiais mais expressivos sobre esse assunto no período de 1985 a 1996 e verificamos que 1261 dos 2811 (44,9%) dos pacientes relatados eram HTLV-I positivos. A média de idade era de 39,5 anos com predominio feminino de 1,9:1. Estes resultados não excluem a causalidade do HTLV-1 como um germe associado a PEIC em todo o mundo.

PALAVRAS-CHAVE: HTLV-I, paraparesia espástica, meta-análise, retrovírus, cofatores ambientais.

Almost a century ago, Strachan described a type of neuropathy from the West Indies[51], and since then different reports resembling Strachan's description have been published throughout the world in which the condition is referred to as tropical spastic paraparesis (TSP)[32]. Although the main foci of TSP patients were initially described in tropical places such as Caribbean countries, Africa and South India[3,6,12,13,32,45], there were also occasional reports from temperate countries such as Chile and Japan[4,37]. We also found, some years ago, an unusual amount of patients who either lived or were born around Southwestern Colombia and presented a Chronic Idiopathic Spastic Paraparesis(CHISPA) which was similar to TSP and which is described elsewhere[42,61-65].

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The history of these CHISPA changed drastically after Poiez et al.[41] discovered, in the earliest 80's, a retrovirus type C called human T lymphotropic virus type I (HTLV-I). Soon thereafter, an association was found between this retrovirus and some types of CHISPA almost simultaneously in both tropical and temperate countries such as Martinique, Jamaica, Colombia and Japan[13,39,43,63]. Subsequently, HTLV-I-associated myelopathy(HAM), as described in Japan by Osame et al.[39], and TSP were considered the same clinical entity[44].

However, despite more than 10 years of intensive research on retrovirus-associated-CHISPA, there is still not a consensus on the etiology of this entity. It is of interest to note that several places with high rates of HTLV-I seropositivity show few, if any, patients with CHISPA; likewise, only 1 out of 1000 infected people with HTLV-I virus develop the clinically manifest disease[52], and clinically similar cases, which are totally seronegative against any retroviral infection, have been found in almost all of those areas where HTLV-I is considered endemic. All of these situations have been puzzling and remain as unsolved questions[62].

In order to get a better knowledge on the epidemiology of this disease and try to obtain more clues to help us in understanding the pathogenesis of this, and probably other diseases associated with this retrovirus, we decided to do a meta-analysis on the main worldwide publications on CHISPA -HAM/TSP- between 1985 and 1996, including our experience. A close review related to this topic was recently presented in a book[62]; however, as far as we know, the data gathered here have not been presented in a peer-review journal yet. We consider that the results found here must be taken into account in further neuroepidemiological studies if we want actually to clarify the pathogenesis of these hidden endemies[45,62,65].

METHODS

The methodology followed in this study was very similar to that recently described by De Castro Costa et al.[8]. We collected and analyzed the papers published on HAM/TSP in international journals from all countries but India, Peru and Japan[48,55,58,62]. For these latter countries the included data were taken from books recently published on this matter. In all countries but India and Zaire the clearest study was chosen for this study[8,9,23,46]. In these two countries two and three papers respectively were included because controversial results have been reported previously. Since papers with at least five patients affected by retroviral infections have impacted the epidemiology of these diseases[38,39] we decided to take into account manuscripts reporting five or more patients with CHISPA. In all but two countries (Thailand, Bangladesh) confirmatory serological tests were commonly performed including the polymerase chain reaction (PCR) method. Because an interesting study analyzing several case-control studies on CHISPA was alredy done we did not think it necessary to perform a similar investigation here[34]. It could happen that some papers were, by chance, ommitted; if so, we apologize to their authors for such mistake as thaught elsewhere[9].

RESULTS

As shown in the Table, there are many cases of CHISPA throughout the world which still remain negative for HTLV-I. It was interesting to note that almost all of those patients from class I area (80% or more of retroviral seropositivity) were black or African natives, belonged to the lower socioeconomic classes, usually lived in rural areas as well as in islands with hot and humid regions such as Seychelles, Zaire, Jamaica, Dominican Republic, Trinidad and Tobago, Southwestern Colombia and Northwest Ecuador, or were inmigrants from the West Indies to United Kingdom. The class II/III areas(40% to 80% of retroviral seropositivity) were found in both tropical and non-tropical regions such as Natal, Martinique, Panama, Venezuela, Chile, Japan and the immigrants from the West Indians to United States. The class IV area(20% to 40% of seropositivity) was formed by mixed populations such as the immigrants from the West Indies to France as well as those from, Peru, West Africa and Brazil. Remarkablely, a minimal amount of black people have been found in Brazil with CHISPA +. The class V area (0-20% of retroviral seropositivity) was surprisingly found in countries located very close to some of those areas with the highest prevalence of retroviral

Table. HTLV-I positive and HTLV-I negative chronic idiopathic spastic paraparesis throughout the world.

COUNTRY	METHOD	SEX (F/M)	AGE	P/T (%)
AFRICA				
TANZANIA	E/IF/PA/WB	0	0	0/61(0.0)
REUNION	E/WB	0/1	59	1/140(0.7)
MOROCCO	E/WB	3/0	38.3	3/40(7.5)
ETHIOPIA	E/IB/IF/EIA/WB	16/6	40.6	2/22(9.0)
IVORY COAST**	E/IF/PA/WB	0/3	31	3/26(11.0)
WEST AFRICA (DALB)	-	-	-	18/82(26.0)
NATAL	E/WB	17/7	-	24/36(66.0)
ZAIRE	E/WB	-	35	26/29(89.6)
	E/PA/WB	-	-	6/10(60.0)
	E/PA/IF/WB	0	2-48	0/33(0.0)
SEYCHELLES**	E/IF	13/7	50	17/20(85.0)
ASIA				
THAILAND	E	2/9	44.7	0/9(0.0)
*INDIA	E/EIA/IF/PA/WB	-	-	4/51(8.0)
BANGLADESH(L)	E	-	-	4/444 (0.9)
*ISRAEL	PA	7/6	57.7	13/-(-)
*JAPAN**	E/PA/WB	415/145	43	589/710(82.9)
OCEANIA				
* SOLOMON ISLANDS	E/WB	0/1	37	1/6(17.0)
AMERICA				
*WE-USA	E/RIA/WB	10/2	54	12/21(57.1)
MEXICO	E/IB/RIA	0	0	0/96(0.0)
CUBA	E/WB/IA	0	0	0/6(0.0)
MARTINIQUE**	E/WB	-	-	10/17(59.0)
JAMAICA**	E/WB	-	40	41/47(83.0)
DREP	E/IF/WB/RIA	-	-	58/62(93.0)
T & T**	E/WB	-	-	8/8(100.0)
*COLOMBIA (SW)**	E/PA/WB	97/51	13-83	148/185(80.0)
ECUADOR**	E/WB	7/3	61	9/10(90.0)
PERU**	E/WB	5/0	46	5/16(31.2)
*PANAMA	EIA/RIA/WB	9/6	44	15/25(60.0)
VENEZUELA	E/IF/WB	3/3	-	6/14(43.0)
*CHILE	E/WB	31/14	40.5	45/85(54.0)
*BRASIL (MA)**	E/PA/WB/IF	149/140	43.8	157/433(36.2)
EUROPE (INMIGRANTS)				
*TO FRANCE	E/IF/WB	7/2	45.7	9/37(24.3)
*TO UK	E/PA/WB	-	57.4	27/30(90.0)
TOTAL		791/406	39.5	1261/2811(44.9)

Legend. Worldwide CHISPA studies by geographical origin. *PCR method, **case-control studies, L, Lathyrism patients; DREP, Dominique republic; T & T, Trinidad and Tobago; SW, south western; MA, meta-analysis; WE, West Indies; DALB, Dakar, Abidjan, Lomé, Ouagadougou; P/T, HTLV-I positive patients /total patients investigated; %, percentage of HTLV-I positive patients. F, female; M, male. The percentage scores of HTLV-.I seropositivity were graded as follows: area I, 0-19%; area II, 20-39%; area III, 40-59%; area IV, 60-79%; area V, 80-100%.

infections and previously described as class I or II/III. It included countries such as Tanzania, Reunion, Morocco, Ethiopia, Ivory Coast, Thailand, India, Bangladesh, Mexico, Cuba, and Solomon Islands.

DISCUSSION

Even though there is a lack of demographic information from some places with CHISPA, it is possible to observe that the data gathered here are quite dissimilar with respect to the presence of retrovirus infection. It was also interesting to observe that there was a predominance of male and mestizo patients in seronegatives CHISPA from Colombia[62,65], unfortunately the lack of data already commented above in both HTLV-I seropositive and seronegative CHISPA prevent us from doing a wider demographic comparison worthy of publication.

Although we agree with the suggestion of using a worldwide common clinical and epidemiological protocol to overcome many gaps found in the different studies performed throughout the world on CHISPA[9], the discrepancies observed in this study do not seem to be due mainly to case definition; nor do we consider that such differences could be due to lack of test sensitivity because the results were re-confirmed by different serological tests including, in several cases, the PCR method, including a still controversial country such as India[7,8,11,12,35,65]. Curiously, in India, very few cases of CHISPA have been found repeatedly associated with HTLV-I infection as reported elsewhere[48]. However, a complete understanding on the dissimilar results reported from places such as Zaire await further clarifications[10,17].

In either case, the uneven distribution observed by us in this study between HTLV-I and CHISPA throughout the world does not preclude the association of HTLV-I with the diseases commented above or, probably with another 20 or more diseases described elsewhere[62]; however, correlation or association does not mean causation. The discrepancy found in these data strongly suggests that the so-called cofactors (named by us distracters) other than HTLV-I infection seem to play an important and definitive role in disease manifestation and evolution[29-31]. Different investigations have suggested that besides HTLV-I infection there are critical genetic or environmental factors that might also be involved in clinically established HAM/TSP, acute T cell leukemia, as well as in mycosis fungoides, Sjögren disease and other diseases associated to HTLV-I infection[2,19,39,40,53,54,56,57,60]. Genetically speaking, it has been considered that HLA haplotypes could be a useful marker for disease susceptibility, mostly in Japanese populations; however, it has not consistently been found in all of those affected groups including the Japanese population itself[1,3,25,32,33,49,50]. Likewise, malnutrition or cassava ingestion are no longer being considered the probable cause of CHISPA in tropical countries[22,26,27].

On the other hand, it has been interesting to observe that the climatic conditions prevalent in the Southwestern Colombia - a CHISPA endemic area - are similar to those present in Equatorial Africa and the CHISPA endemic areas of the so-called "temperate" places of Japan and Chile[27,29,30,64]. Such environmental situations - some of which have been appreciated directly by these authors - modify local hygienic conditions and particular nutritional habits present in the foci of CHISPA[20,21,24,26,28]. These environmental circumstances might explain, therefore, not only the picture of HTLV-I-associated-CHISPA but also the clinically similar but persistently seronegative diseases described at the same time, by the same group of researchers investigating in the same retroviral endemic area[9,14,15,42,48,49,65], and they would lead patients to a widespread toxic-metabolic neurodegeneration. Thus, hygienic and nutritional habits modified by the surrounding environment might produce a latent and subclinical state of immunodeficiency allowing this, and possibly other, retroviral infections to act - if any - opportunistically in the exposed populations[5,20,21,59]. The lack of refrigeration as well as the mycotoxin intoxication found recently by our group in patients with CHISPA regardless of their retroviral status support this view[26,28]. Therefore, efforts in identifying environmental factors, should continue because they could be the real aetiological agents in this and likely other pathologies associated to retroviral infections, and, likewise, they seem to be extremely

important in understanding the multistep carcinogenesis, neurodegeneration and oncogene activation described not only in CHISPA and ATL[16,18,36,42,47] but in the other degenerative disorders associated with but not caused by HTLV-I infection throughout the world.

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