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Profile of Caucasian Women with Possible Genetic Predisposition to Reflex Sympathetic Dystrophy: A Pilot Study

*Angela Mailis, M.D., M.Sc., F.R.C.P.C. (Phys. Med.) and †Judith Wade, B.Sc.

**Pain Investigation Unit, Department of Medicine, and †HLA Laboratory, The Toronto Hospital, Toronto, Ontario, Canada*

Abstract:

Objectives: To test possible human lymphocyte antigen (HLA) associations in subjects with reflex sympathetic dystrophy (RSD), and to determine correlation of HLA associations to treatment outcomes.

Design: Identification of class I (HLA-A, B, C) and class II (HLA-DR and DQ) (MHC) antigens by well-defined reagents in patients with RSD.

Setting and Patients: The HLA analysis was performed on 15 Caucasian women attending a university pain clinic and diagnosed with RSD on the basis of strict inclusion and exclusion criteria.

Outcome Measures: Resistance to treatment was defined on the basis of lack of response to conservative management, failure to experience long-term symptom relief after sympathetic blocks, recurrence of pain after sympathectomy, need for palliative treatment, and degree of residual disability at the end of all treatments.

Results: A twofold increase of A3, B7, and DR2(15) MHC antigens was observed in the study population compared to control frequencies. Eighty (five of six) of DR2(15)-positive patients proved to be resistant to treatment.

Conclusions: The results of this pilot study are the first to suggest a possible genetic diathesis in RSD patients with poor treatment outcome. If this finding can be confirmed in larger studies, strictly defined RSD could constitute the third neuroimmune disorder (besides multiple sclerosis and narcolepsy) associated with DR2(15). Gene(s) conferring susceptibility to RSD may be present within or near the MHC region of the short arm of chromosome 6. Due to the small size of our study group it is imperative that larger studies be done in RSD patients employing strict diagnostic criteria to confirm or refute our original observations.

Key Words: RSD—MHC HLA—Resistance to treatment.

Reflex sympathetic dystrophy (RSD) is a term currently describing (1) a complex disorder or group of disorders resulting from limb trauma (very frequently trivial) with or without obvious nerve lesion, visceral diseases (e.g., after myocardial infarction or spinal cord injury), central nervous system (CNS) lesions (e.g., stroke), and rarely without any antecedent event. This painful syndrome appears with sensory abnormalities, disturbances of the limb blood flow and sweating, trophic changes, and movement disorders. It is not necessary that all components of the syndrome coexist (1).

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Address correspondence and reprint requests to Dr. A. Mailis, Director, Pain Investigation Unit, The Toronto Hospital (Western Division), #328-11MP, 399 Bathurst Street, Toronto, Ontario, Canada M5T 2S8.

There is significant controversy as to the actual definition, diagnosis, etiopathogenesis, and treatment of the syndrome. Ochoa (2) has repeatedly raised the point that "the term RSD is a purely descriptive taxonomic term for a nonspecific symptom–sign complex derived from a variety of pathophysiological states, with the non-organic causes of RSD being the most common."

The terms sympathetically maintained pain (SMP) and sympathetically independent pain have been introduced by Roberts (3) and Campbell et al. (4), respectively, to define pain that is dependent or independent of the involvement of the sympathetic nervous system (SNS). These terms are rather empirical and not mechanistic or etiological attempts for categorization. While the terms are not synonymous with RSD and do not necessarily indicate subsets of RSD, they are used quite commonly, adding to the confusion surrounding the syndrome.

No single pathophysiologic mechanism over the past century has been able to completely explain all the clinical features of RSD or account for the multiple etiologic factors "initiating" the syndrome. However, "mirror" phenomena, spreading, migration to the contralateral limbs, and recurrences have been described (5–7), as well as generalized abnormalities beyond the affected limb(s) (8,9). Greipp and Thomas (10) described three families with two or more members affected by RSD. Despite the existence of potentially different etiopathophysiological entities (11), we felt that the rather homogeneous clinical symptom/sign complex (that has been the hallmark of RSD over several decades of debate) may be associated with a specific predisposition, or "diathesis." Devor and Raber (12) provided evidence for heritability of autotomy associated with pain in an experimental rat model of neuropathic pain (giving impetus to our idea that maybe other pain syndromes could also have a genetic component). Therefore, we designed this study to look for associations between RSD and specific major histocompatibility complex (MHC) human lymphocyte antigens (HLAs) in a well-defined patient population.

METHODS

Class I (HLA-A, B, C) and class II (HLA-DR and DQ) MHC antigens were identified in 15 Caucasian) women with RSD by well-defined serologic reagents in the standard National Institutes of Health compliment-dependent microtoxicity assay. We elected to test Caucasian women only (quite prevalent in our RSD population) in an attempt to create the most representative and homogeneous study group. The place of birth of each patient as well as the place of birth of father and mother were ascertained. The frequencies were compared to those of a control Caucasian population (13).

The diagnosis and classification of RSD was based on detailed protocols and scoring systems used in our institution (14). We have arbitrarily used the term "physiogenic" RSD (for lack of a better or more suitable term) to indicate a painful and homogeneous complex of signs and symptoms arising from derangement of sudomotor, vasomotor, and trophic (superficial and deep) tissue mechanisms in patients fulfilling all of the following criteria.

Inclusion criteria

These included the presence of pain and documented sensory, sudomotor, and/or dystrophic changes (radiological and electrophysiological abnormalities were helpful but not necessary for the diagnosis), and consistently reproducible responses to multiple sympathetic/phentolamine blocks and/or nerve blocks, but negative responses to placebo testing.

Exclusion criteria

These were the presence of potential RSD imitators (vascular, inflammatory, or infectious diseases), and the presence of serious psychiatric disorders and intense pain behavior producing limb immobilization, or the presence of factitious disorders or malingering.

Findings supportive of but not critical for the diagnosis of RSD included abnormalities in the three-phase bone scan (TPBS), arterial doppler duplex ultrasonography and plain x-rays. The TPBS was considered typical or diagnostic for RSD if there was distinct periarticular uptake of the radiotracer in all of the joints of the involved hand or foot in the delayed phase. The TPBS was considered suggestive for RSD when there was increased delayed tracer uptake in several but not all the joints of the involved extremity in a periarticular manner. An abnormal ultrasonography pattern in patients with RSD has been described before (6,15) and consists of loss of triphasic wave form, significantly increased diastolic flow and decreased pulsatility index (highly suspicious of RSD/SMP if the pulsatility index is <2). Osteopenia was documented in plain or high-resolution radiographs. Also, electromyographic and nerve conduction studies were per-

formed in those patients who could tolerate the test to determine nerve or nerve root injury (RSD/causalgia). Inflammatory, vascular, and other disorders that could potentially imitate RSD were excluded by appropriate studies using a multidisciplinary, multiconsultation approach.

Responses to sympathetic blocks (three or more blocks over time) were judged for consistency and reproducibility of results on the basis of pain relief obtained either on a visual analogue scale (10 cm long) or a verbal pain scale (0–10), with simultaneous documentation of alteration of sensory abnormalities (e.g., allodynia). Local sympathetic blocks were validated through temperature alterations in the absence of somatic blockade. Intravenous phentolamine blocks were performed with 30–45 mg of phentolamine infused over 30 min, preceded by a 1–2-h normal saline infusion (presented as active drug) to test for inert placebo responses.

All patients underwent lengthy behavioral observations under distraction (when they did not know they were under observation) and during confrontational testing (when they knew they were being examined) to document consistency of behavior (e.g., use of affected limb, pain avoidance, or withdrawal from touch). All patients were submitted to formal psychological and/or psychiatric evaluations. These included psychiatric interview, and psychological consultation and personality profile analysis or both.

"Residual disability" (at the end of all treatments) was classified on the basis of a scoring system as follows: ability to perform the same occupation as prior to RSD, 0; decreased work ability, 1; and unable to work, 2. The ability to perform the same household chores as prior to RSD was 0; decreased household ability, 1; and severe restrictions, 2. The ability to engage in the same leisure activities as prior to RSD was 0; decreased leisure ability, 1; and severely restricted, 2. Patients with scores of 0 were classified as having no disability, 1–2 as mildly disabled, 3–4 as moderately disabled and 5–6 as severely disabled.

"Resistance to treatment" was classified (without prior knowledge of HLA findings) on the basis of the following scoring system: response to conservative management (very good response, 0; poor response, 1), symptom relief (>6 months) from sympathetic blocks, if there was a positive response to sympathetic blockade (yes, 0; no, 1), recurrence of pain after sympathectomy (no, 0; yes, 1), need for palliative treatments, i.e., narcotics, spinal stimulation, etc. (no, 0; yes, 1), and residual disability after final treatment (none, 0; mild, 1; moderate, 2; severe, 3).

The maximum possible score for resistance to treatment was 7. If one of these factors was not present, for example, if the patient's pain was not responding to sympathetic blocks, the term nonapplicable was applied. With this scoring system patients with poor response to sympathetic blocks could have a lower score.

RESULTS

Patient clinical profiles

The patient group consisted of 15 Caucasian women sequentially admitted to the study on the basis of fulfilling both inclusion and exclusion criteria from our larger population of RSD referrals. Eleven patients were born in Canada (eight of English Canadian, two of French Canadian, and one of eastern European parents). Regarding the remaining four patients (and their parents), one was born in England, two in eastern Europe, and one in Italy. No patient was of Jewish, Spanish, or Arabic ancestry (at least as far as their parents and the patients were concerned). The HLA results were analyzed only when it was determined that all possible treatments had been exhausted and the patients' current disabilities were residual. The patients' mean age was 39.5 years (range, 18–72). However, 11 of 15 patients were <49 years old (73%). Mean symptom duration (from pain onset to the time of consultation at the Pain Unit) was 15 months (range, 2 months to 3 years). However, four of 15 patients had been diagnosed as suffering from RSD prior to their referral to our pain unit, and previous treatments (including sympathetic blocks in some cases) had been given fairly early in the course of their disorder. A single lower extremity was involved in 11 cases and a single upper extremity in two cases, and two patients had multiple limb involvement (both lower extremities in one patient and both lower and one upper extremity in another patient). In 13 cases, trauma (fracture in six and soft-tissue injury in seven) preceded the onset of symptoms, while spontaneous RSD occurred in the two patients with multilimb involvement. Two patients (of 10 tested patients) with traumatic RSD had persistent electrophysiologically documented peripheral nerve or root injury (RSD/causalgia). The bone scan was diagnostic of RSD in seven patients and suggestive of RSD in another five pa-

tients. Arterial Doppler ultrasonography demonstrated highly abnormal diastolic flow consistent with peripheral vasodilatation (RSD pattern) in the involved limbs of three patients. Osteopenia of the affected extremities was demonstrated radiographically in eight patients.

Overall, three patients had claims with Worker's Compensation, and four patients had pending litigation as a result of a car accident (44% of all patients). These figures are similar to those in the general pain patient population in our Pain Unit (16). One patient was transferred from the psychiatric ward (where she had been hospitalized for psychogenic seizures) when she accidentally fractured her leg, leading to RSD development (case 15), and four patients had depression relating to significant life stressors (cases 5, 10, 12, and 15). One patient (case 4) was found to have a passive, dependent personality. Despite underlying depression in a few individuals, no patient was believed to display exaggerated pain behavior or immobilize the involved limb (as the vast majority of patients were suffering from lower-limb RSD and were all ambulatory without aids, with the exception of case 4). In all patients the response to blocks and placebo testing was considered appropriate, indicating a physical disorder.

Response to sympathetic blocks

In response to multiple diagnostic sympathetic blocks and phentolamine testing, 11 patients proved to have consistently more than 75% pain relief, two 50–75% pain relief, and one 50% pain relief. One patient with documented peripheral nerve injury failed to respond to the sympathetic blocks. No patient had positive response to placebo (as per the admission criteria to the study). In the group of 11 patients with more than 75% pain relief after serial sympathetic blocks with a local anesthetic, seven patients experienced short-term improvement (hours) and four patients experienced excellent long-term relief. In one case, the pain recurred after 9 months and necessitated surgical sympathectomy (case 10), which ultimately failed. In the remaining three cases (patients 12, 14, and 15), the relief had been sustained at the latest follow-up examination (>1 year). Details of the patient group are shown in Table 1.

Treatment outcomes

Ten patients had a poor outcome at the end of all treatments and their mean resistance-to-treatment score was 6.1 (range, 4–7). These resistant-to-treatment patients had a failed surgical or chemical sympathectomy (eight of eight), required trial or permanent implantation of spinal cord stimulation (five of 10), and needed oral or infused narcotics (10 of 10) in 6–12 months of follow-up checks after the final intervention. The mean duration of symptoms in this group (from onset to the time of consultation at the pain unit) was 16.3 months (range, 2 months to 2.5 years). However, the mean duration of symp-

TABLE 1. *Clinical patient data*

Case	Age, yr (limb)	Symptom duration	RSD cause	Pain features	Symptom/sign complex	TPBS	Doppler	Osteopenia
1	18 (RL,LL)	6 mo	Spontaneous	C,A,P	Co,Al,Hy,BT,Dy	RSDd	RSDs	No
2	26 (LL)	2 yr	Knee sprain	C,B,T	Co,Al,Hy,BT,Dy	NRSD	Not done	No
3	23 (RA)	2 mo	Overuse	C,B	Co,Al,Hy,BT,Dy,E,S	RSDd	N	Yes
4	23 (RL,LL,LA)	3 yr	Spontaneous	C,B	Co,Al,Hy,BT,Dy,S	RSDs	N	Yes
5	56 (LL)	10 mo	Ankle fracture	C,B	Al,BT,Sv	RSDd	N	Yes
6	18 (LL)	4 mo	Ankle sprain	C,B	Co,Al,Hy,BT,Dy,E,S	RSDs	N	Yes
7	72 (RL)	2 yr	Knee surgery	C,B	Co,Al,Hy,BT	NRSD	N	Yes
8	60 (RL)	2.5 yr	Femoral fracture	C,B	Al,Hy,BT	RSDd	N	Yes
9	40 (RL)	2 yr	Leg fracture	C,A,T	Al,Hy,BT,Nu	RSDd	N	No
10	48 (RA)	3 mo	Br pl inj	C,B,A	Ho,BT,Dy,E,S,Nu,Tr	RSDd	RSDs	Yes
11	37 (LL)	3 mo	Knee sprain	C,B	Al,Hy,BT,Sv	RSDs	N	No
12	34 (RL)	13 mo	Leg fracture	C,B	Al,Hy,BT,Sv	RSDs	RSDs	No
13	64 (RL)	3 yr	Knee trauma	C,A	Co,Al,Hy,Tr	NRSD	N	No
14	31 (LL)	4 mo	Ankle fracture	C,A	BT,Sv,Hy	RSDs	N	Yes
15	43 (LL)	5 mo	Foot fracture	C,B	Ho,Hy,BT,S	RSDd	N	No

RSD, reflex sympathetic dystrophy; TPBS, three-phase bone scan; RL, right leg; LL, left leg; C, constant; A, aching; P, piercing; Co, cold; Al, allodynia; Hy, hyperalgesia; BT, bone tenderness on palpation of the long bones of the symptomatic limb; Dy, dystrophy (wasting contractures, altered skin texture); RSDd, RSD diagnostic; RSDs, RSD suggestive; B, burning; T, throbbing; NRSD, abnormal but non-RSD pattern; RA, right arm; E, edema; S, sweaty; N, normal; LA, left arm; Sv, history of sudomotor changes; Nu, numbness; Ho, abnormally warm; Tr, tremor.

Patient 9 had documented superficial peroneal nerve damage, and patient 10, C6 and 7 root damage.

toms from the time of pain onset to the time of sympathectomy was 17.4 months (range, 4–24 months) in the group of eight patients who underwent sympathectomy.

Five patients had an excellent treatment outcome and were classified as non-resistant to treatment (mean resistance-to-treatment score, 2; range, 1–3). One needed surgical and one chemical sympathectomy (both with excellent pain relief at follow-up observation of 8–12 months). The remaining three patients in this group had responded very well to serial sympathetic blocks and a combination of conservative treatments at >1 year follow-up check with no symptom recurrence. The average duration of symptoms in this group was 12.2 months (range, 3–36 months). However, the durations of symptoms from the time of pain onset to the time of sympathectomy were 7 and 44 months, respectively, in the two who underwent sympathectomy. Table 2 provides details of resistance-to-treatment scores.

HLA profile analysis

In summary, considerably different MHC antigen frequencies were noted in the RSD patient population when compared to the controls (expressed as the percentage of antigen occurrence in the RSD patients versus normal controls): A3, 40 versus 20.6; B7, 40 versus 17.7; DR2(15), 40 versus 19.9; and DR4, 13.3 versus 23.6. None of the antigen frequencies in the patient group (due to small sample size) was statistically different when compared to the tabled control frequencies by Fisher's exact test. Remarkably, five of six patients positive for DR2(15) (DR15 and DRW15) had resistance to treatment (constituting 50% of the resistant-to-treatment group), while only one of six patients with DR2(15) did quite well with treatment (constituting only 20% of the non–resistant-to-treatment group). These results again did not reach statistical significance. It is worth noting that the only DR2(15)-positive patient with an excellent long-term outcome was the patient with psychogenic seizures and accidental leg fracture complicated by RSD (indicating that underlying depression and personality profile did not hinder her recovery). The HLA-detailed profiles and their relation to resistance to treatment are shown in Tables 3 and 4.

TABLE 2. *Resistance to treatment*

Patient	A	B	C	D	E	Score
Group 1: treatment-resistant patients						
1	1	1	1	1	2	6
2	1	1	1	1	3	7
3	1	1	1	1	3	7
4	1	1	1	1	3	7
5	1	1	1	1	3	7
6	1	1	1	1	2	6
7	1	1	1	1	2	6
8	1	1	N/A	1	2	5
9	1	N/A	N/A	1	2	4
10	1	1	1	1	2	6
Total score						6.10
Group 2: non–resistant-to-treatment patients						
11	1	1	0	0	1	3
12	1	0	N/A	0	1	2
13	1	1	0	0	1	3
14	1	0	N/A	0	0	1
15	1	0	N/A	0	0	1
Total score						2.00

A, response to conservative treatment (0, good response; 1, no response); B, long-term relief with sympathetic blocks (0, yes; 1, no); C, recurrence of pain after sympathectomy (0, no; 1, yes); D, need for palliative treatment (0, no; 1, yes); E, residual disability after final treatment (0, none; 1, mild; 2, moderate; 3, severe). N/A, not applicable.

TABLE 3. *HLA profile of RSD patients vs. those resistant to treatment*

Case	A3	B7	DR2 (15)	DR4	Resistance to treatment
1	—	—	Yes	—	Yes
2	Yes	—	Yes	—	Yes
3	—	—	—	Yes	Yes
4	Yes	—	—	—	Yes
5	—	—	—	—	Yes
6	—	Yes	Yes	—	Yes
7	Yes	Yes	Yes	—	Yes
8	—	—	—	—	Yes
9	—	—	Yes	—	Yes
10	—	Yes	—	—	Yes
11	—	—	—	—	No
12	Yes	Yes	—	Yes	No
13	Yes	Yes	—	—	No
14	—	—	—	—	No
15	Yes	Yes	Yes	—	No

HLA, human lymphocyte antigen; RSD, reflex sympathetic dystrophy.

DISCUSSION

The principal finding of this pilot study was the clustering of DR2(15) antigen in patients with RSD who seemed to have poor outcome to treatment (high resistance to treatment).

Patient characteristics and profiles

It is apparent that the study patients fall into two etiological classes: nonneural tissue RSD (a term used to indicate the absence of detectable nerve or

TABLE 4. *MHC HLA profile of the study group*

Patient	
1	A1, A25, BW57, B35, CW4, −, DR1, DRW15, DQW1
2	A2, A3, BW62, B35, CW3, CW4, DRW15, DR7, DRW53, DQW1, DQW3
3	A1, A11, B8, B35, CW4, DR4, DR7, DRW53, DQW3
4	A2, A3, B51, BW61, DR1, DRW17, DRW52, DQW1, DQW2
5	A2, A32, B44, B51, CW5, DR7, DRW6, DRW52, DRW53, DQW1, DQW3
6	A2, A-, B7, B44, DRW15, −, CW5, CW7, DRW52, −, DQW1, −
7	A3, A24, B7, B-, CW7, DRW15, DR-, DQW1
8	A26, A30, B49, B13, CW4, DR1, DR7, DR53, DQ1, DQ2
9	A2, A26, BW62, BW61, CW3, DRW15, DRW17, DRW52, DQW1, DQW2
10	A2, A24, B7, B8, CW7, −, DR1, DRW17, DRW52, DQW1, DQW2.
11	A2, A32, B51, BW61, CW2, −, DRW61, −, DRW52, −, DQW1, DQW3
12	A3, A11, B7, B35, BW4, CW4, CR4, −, DRW53, DQW3, −.
13	A3, A−, B7, B60, CW3, DR17, DR6, DR52, DQ2, DQ1
14	AW34, A32, BW62, BW63, CW3, DRW11, CRw14, DRW52, DQW1, DQW3
15	A1, A3, B7, B8, BW6, DR15, DR17, DR52, DQ1, DQ2

MHC, major histocompatibility complex; HLA, human lymphocyte antigen.

Patients 1–10 belong to the treatment-resistant group. DR15 and DRW15 (DR2(15)) are underlined.

nerve root injury), either traumatic after bone or soft-tissue injury (n = 11) or spontaneous (n = 2), and RSD/causalgia (in the presence of nerve or nerve root injury) (n = 2). We have satisfied ourselves on the basis of strict inclusion and exclusion criteria that irrespective of different etiopathogenetic mechanisms, the patients were suffering from a physical (and not psychological) disorder, and that the symptom/sign complex was not the result of some detectable vascular, inflammatory, or other RSD imitator or mere immobilization. In the two patients with detectable nerve injury, the limb findings were quite diffuse, extending outside the territory of involved nerve(s). Therefore, we felt we were justified to include these patients in the study population.

In terms of response to sympathetic blockade, 13 patients were classified as sympathetic block responders, one patient as a mixed block responder with only 50% pain relief to repeated sympathetic blocks, and one patient with nerve injury as a non-responder to sympathetic blocks. This classification led to sympathectomy in 10 of 15 patients.

In our pilot study, the clinical severity of RSD was not different between the treatment-resistant and treatment-responsive patients. As well, underlying depression or compensable claims did not seem to influence treatment outcome. One may argue that the better outcome of the non–resistant-to-treatment group was due to their earlier treatment in our clinic. However, five patients in the resistant-to-treatment group (cases 1, 3, 5, 6, and 10) came to us with a mean symptom duration of 5 months only (range, 2–10 months). In addition, case 2 had already received multiple blocks prior to her attendance at our Pain Clinic. Despite early aggressive interventions (such as physical therapy, nonsteroidal anti-inflammatory medication, prednisone, and sympathetic blocks), even the patients treated early in the resistant-to-treatment group ultimately remained considerably disabled.

Therefore, our patient group seems to be typical of the RSD population described in the literature (multiple etiologic factors and variable response to sympathetic blocks and other forms of treatment). Emphasis, however, was placed on the fact that we have satisfied ourselves as to the physical and not psychological origin of the initial symptoms and signs.

General discussion

Rheumatoid arthritis and diabetes mellitus have been identified to be associated with class II HLA antigens, while ankylosing spondylitis and Reiter's syndrome have been associated with class I HLA antigens. Two CNS disorders (multiple sclerosis, (MS) and narcolepsy) have also been associated with DR2(15). In a recent article (17), the presence of HLA-DR2 in patients with MS was associated with resistance to myelin treatment, in contrast to MS patients who lacked the HLA-DR2 antigen, even if the study did not specifically identify DR2(15) or DR2(16).

A questionnaire administered to 1,348 individuals who have RSD and are registered with the Reflex Sympathetic Dystrophy Syndrome (RSDS) Association in the United States (18) confirms female sex prevalence (female/male ratio, 3.5:1), Caucasian prevalence (94.4%), and northern European prevalence (63%). These data may be flawed with several errors and selection bias. Are all patients in the RSDS Registry suffering from true "physiogenic" RSD or some other disorder? How has the diagno-

sis been made? Could the high female/male ratio be merely due to the fact that "women complain more and seek health care more," or does it relate to female gender prevalence? What is the explanation for the striking absence of blacks and Orientals from the RSDS Association Registry? Could this happen on the basis of selection bias, or could it be due to the rare occurrence of RSD in these ethnic groups?

With regard to the latter questions, we have ourselves made the observation that there is indeed significant female prevalence (approximately 3–4:1 according to our records of last year's documented RSDs). There is also a striking absence of Orientals and blacks in our RSD population with "physiogenic" RSD (as per our criteria and for lack of better term), despite the considerable numbers of these two ethnic groups attending the orthopedic/fracture clinic (which accounts for >50% of all our RSD referrals and serves a general population).

The clustering of 80% of DR2(15)-positive patients (five of six) in the treatment-resistant group is an exciting finding that (if confirmed) will constitute the first data in the literature to suggest an association with specific MHC HLA antigens and possibly a genetic contribution to the pathogenesis of the clinical complex of "physiogenic" RSD. Specifically, our data may indicate that the presence of DR2(15) may be associated with resistance to treatment irrespective of the severity of clinical appearance. Due to the small size of the sample, these results could also be due to mere chance. It is imperative therefore that further and larger studies be done in well-defined groups of patients with "physiogenic" RSD and in informative families with both affected and unaffected members to confirm or refute our original observations. Due to the controversies surrounding the diagnosis and the pathophysiology of the syndrome, strict diagnostic criteria (particularly in terms of placebo testing and exclusion of psychiatric/factitious disorders, as well as other disease imitators) will have to be applied in the populations to be examined. Such diagnostic criteria are mandatory, since it is indeed our experience that similar clinical appearance can occur in some patients who exhibit severe pain-avoidance behavior and intensely immobilize the painful limb or can be self-induced (as part of a factitious disorder).

If our initial observations are confirmed, "physiogenic" RSD could be the third neurological (neuroimmune) disorder associated with the MHC antigen HLA-DR2(15). Gene(s) conferring susceptibility to development of RSD and/or resistance to treatment may be present within or near the MHC region of the short arm of chromosome 6. Variable pathogenetic mechanisms (soft-tissue trauma, nerve injury, CNS dysfunction, etc.) could result in local release of tissue components (which are usually compartmentalized/sequestered to self- and non–self-recognition). In patients genetically predisposed to respond to "self tissue," variable responses to injury and release of circulating mediators can promote a cascade of reactions affecting the involved limb (and potentially other limbs). Conversely, the presence of disease susceptibility gene(s) may alter the expression and interaction of primary afferents with the target sites. Support for this hypothesis may be rendered by the findings of Drummond et al. (9), who noticed the presence of neuron-specific enolase immunoreactive microneuromas in four symptomatic and two asymptomatic limbs of RSD patients.

A genetic (but not necessarily inherited, in the case of new mutations) diathesis or predisposition may explain the triggering of similar clinical appearance by variable, unrelated, or at times trivial lesions in selected individuals only; the potential for different peripheral and/or central pathophysiologic mechanisms to exist independently or coexist; the variable responses of patients to different forms of treatments including sympathetic blocks and sympathectomy; the migration, spreading, recurrences, or familial occurrences of the syndrome; and race and/or gender differences.

If our original observations can be duplicated in larger studies, serologic and molecular techniques may help identify a subpopulation of patients with genetic susceptibility to "physiogenic" RSD and/or resistance to treatment. Recognition of such a group may assist in determining the value of preventive and current therapeutic interventions in RSD.

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