Prevalence Study

Prevalence of Complex Regional Pain Syndrome in a Cohort of Multiple Sclerosis Patients

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Background: More than 50% of multiple sclerosis patients experience chronic pain syndrome. We set out to determine the specific type of chronic pain that was seen in our multiple sclerosis patients.

Methods: Patients with multiple sclerosis were catalogued between January 2002 and April 2006 and identified by a search of the database. Only MS patients that met the 2005 revised McDonald criteria were included.

Results: We determined the prevalence rate of complex regional pain syndrome in a cohort of multiple sclerosis patients. In our sample of 205 multiple sclerosis patients, the prevalence of complex regional pain syndrome was 4 cases per 205 compared to an expected age and sex-adjusted total prevalence of 0.078 cases per 205 ($p < 0.0001$).

Conclusion: This study suggests that multiple sclerosis patients are at a higher risk of developing complex regional pain syndrome than the general population.

Key words: Multiple sclerosis, complex regional pain syndrome, prevalence

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More than 50% of multiple sclerosis (MS) patients experience chronic pain syndromes, such as dysesthetic extremity pain, back pain, painful leg spasms and visceral pain (1). We were interested in a specific type of chronic pain seen in our MS patients, namely, complex regional pain syndrome (CRPS). To our knowledge, only one case of CRPS with concomitant MS is documented in the literature (2). Although CRPS most commonly occurs after trauma to soft tissue or peripheral nerves, approximately 10% of patients have documented central nervous system lesions as the initiating cause (3). Therefore, we investigated the prevalence of CRPS in a small cohort of MS patients.

Methods

Patient Selection

All patients with MS, catalogued between January 2002 and April 2006, were identified by a search of the computerized database of author RJS. Patients were drawn from his general neurology clinic, not a

pain clinic. Only MS patients that met the 2005 revised McDonald criteria for diagnosis of MS were included in the study (4). Excluded from the study were patients with isolated cases of optic neuritis and patients receiving a diagnosis of CRPS prior to MS.

To identify cases of CRPS within the MS population, we again searched the computerized database. Each chart was reviewed and only patients that satisfied the 2005 modified research diagnostic criteria for CRPS as established by the International Association for the Study of Pain were included in the study (5). There was no clinical difference in CRPS as regarding factor analysis of signs and symptoms of CRPS in the MS patients versus those with peripheral etiologies. Four patients with MS developed CRPS and were referred to our CRPS center specifically for treatment of this condition. They were excluded from this study as our goal was to evaluate the prevalence of CRPS in a general MS cohort and to eliminate referral bias as Drexel is a major center for retreatment of CRPS.

The institutional review board of the Drexel University College of Medicine approved the review of medical charts. One author (CG), reviewed all medical charts and another author (RJS) confirmed the diagnosis of CRPS and MS in all patients.

Statistical Method

We calculated a predicted prevalence rate of CRPS in an MS population based on the only CRPS population data available from the United States (6). From our data, we obtained an actual prevalence rate of CRPS in this cohort of MS patients. The only incidence and prevalence data for CRPS were generated from the population of Olmstead County, Minnesota (1990 population of 106,470) (6). This data demonstrated a female: male ratio of 4:1, an incidence rate of 5.46 per 100,000 person years at risk and a period prevalence of 20.57 per 100,000. Utilizing this baseline data, we calculated the expected incidence of CRPS in a population of 205 MS patients. Simple division of the MS cohort studied 205 patients into the population based calculations from Sandroni et al's (6) study predict less then one patient in this number of patients would be expected to have CRPS if there was no comorbidity between the diseases. Conversely, the total number of MS patients in our active CRPS data base of 494 patients is 8 which is a prevalence of 1.6%, dramatically higher than expected.

Results

For the study, 208 MS patients fulfilled diagnostic criteria. Of these, 7 patients satisfied the new diagnostic criteria for CRPS. Four of the CRPS patients were excluded from the study due to a referral bias, since Drexel is a referral center for CRPS. The total number of MS patients studied was 205 and the number of MS patients with CRPS was 4 due to the above noted exclusions.

For our MS sample of 205 patients, the age and sex-adjusted expected prevalence of CRPS was 0.00673 cases in males and 0.0723 cases in females; total 0.078 cases (Table 1). Note that these are the expected num-

Table 1. *Expected prevalence of CRPS in MS patients.*

	Men		Women	
Age (years)	No. of patients	Expected prevalence of CRPS (number of cases)	No. of patients	Expected prevalence of CRPS (number of cases)
30–39	10	0	22	0.0131758
40–49	23	0.002438	51	0.0206652
50–59	15	0.002457	47	0.021667
60–69	7	0.001835	16	0.0115936
70–79	0	0	3	0.001872
80–110	1	0	1	0.0003702
Total	58	0.00673*	147	0.0723

*The values are very small because Sandroni et al found rates on the order of 20/100,000 or less. We expect less than even a single case in our entire sample of 205. CRPS = complex regional pain syndrome.

Table 2. *Characteristics of four patients with MS and CRPS.*

Sex/age	Time from diagnosis of MS to CRPS	Form of MS	Clinical features of MS	MRI findings
Female/ 49 years	3 years	Secondary progressive	Impaired cognition, short term memory loss, right-sided weakness, blurred vision	Lesions in left occipital lobe, left posterior parietal white matter, and at C7
Female/ 51 years	2 months	Relapsing remitting	Optic neuritis, bowel and bladder incontinence, ataxia, bilateral lower extremity weakness	Lesions in splenium, periventricular white matter, right temporal horn, left parietal white matter, bilateral corona radiata, ventral lesion from C3-4 disc space to C5, dorsal lesion from T3-T5
Female/ 51 years	20 years	Secondary progressive	Bilateral arm and leg paresthesias, blurred vision, ataxia	Lesions in periventricular white matter and centrum semiovale at C2-3 disc space
Female/ 32 years	8 years	Relapsing remitting	Ataxia, blurred vision, dizziness, bladder incontinence	Lesions in periventricular white matter, bilateral corona radiata, left parietal white matter, left cerebellar hemisphere

CRPS = complex regional pain syndrome.

bers of patients, not the rate per 100,000. Since Sandroni et al (6) found rates of less than 20/100,000 for CRPS in a general population, our estimate of the expected number of CRPS patients in a cohort of 205 MS patients would be very small. Our actual total number of cases of CRPS in MS patients was 4 per 205 ($p < 0.0001$, using an exact binomial calculation in which the expected female rate was applied to the whole sample to be conservative). All patients with combined MS and CRPS were female whose age at onset ranged from 32 to 51 years with a mean of 45.7± 9 SD; median, 50.

As shown in Table 2, the time from diagnosis of MS to CRPS varied widely, and the latter diagnosis was found in patients with both secondary progressive and relapsing-remitting MS. The number of cases is too small to draw any conclusion beyond that the syndrome is not restricted to one form of MS.

Conclusion

This is the first study reporting the prevalence of CRPS in MS patients. The prevalence rate of 4 CRPS cases per 205 MS patients is considerably higher than the expected prevalence rate of 0.078 cases per 205 MS patients. Our data from this limited study suggests that MS patients have a higher risk of developing CRPS than the general population.

To date, only one case report addresses CRPS as a possible complication of MS (2). The authors suggest that the formation of a syrinx, the result of a degenerating plaque, disrupted the sympathetic flow in the cervical cord leading to CRPS (2). Recent experimental and clinical data supports the hypothesis that neuropathic pain caused by peripheral or central nervous system injury can be initiated and maintained from activation of immune cells and their inflammatory mediators (7). We suggest that the higher than expected incidence of CRPS in MS patients is related to demyelination of spinothalamic or other pain pathways rather than both illnesses sharing a common immunological pathogenesis.

The limitations of this study are its small size, possible referral bias, and uncertainty in estimating the true prevalence of CRPS in the United States. Any MS patient referred to the general neurology clinic for pain was eliminated from the study in an effort to minimize referral bias. Therefore, all MS patients with CRPS were initially pain free and developed CRPS over time. This form of CRPS is caused by a CNS injury; therefore, the distinction between CRPS Type I where pain cannot be traced to an identifiable nerve injury and Type II, when pain can be traced to a nerve injury, is not relevant since it pertains to the presence of a major peripheral nerve injury. We employ the 2005 proposed research criteria for CRPS (5) in our study because it boasts a high specificity of 0.96 and a sensitivity of 0.70.

All of these patients received standard therapy for CRPS which included NSAIDs, antidepressants, anticonvulsants, and opioids. All had undergone sympathetic blockade. All had undergone subanesthetic treatment with ketamine (150 mg IV over 4 hours, 0.1 mg clonidine, and 4 mg of midazolam) daily for 10 days with success (8). We have noted no difference in response to treatment of CRPS in MS patients compared to patients with the usual peripheral traumatic etiologies and therefore we employed our standard protocols for these patients. The immunomodulating agents that these MS patients utilized had no bearing on their course or response to treatment. The small sample size possibly explains the lack of men with both CRPS and MS. Ideally, prevalence data of CRPS from Philadelphia or Pennsylvania would have been used to calculate expected prevalence values; however, the only study available for comparison was conducted in Olmstead, Minnesota (6). A prospective long-term study of MS patients evaluating the development of CRPS may yield a more accurate prevalence calculation.

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